INTERNATIONAL STANDARDS FOR CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION

Fifth Edition
March 2012

NOTICE

These Standards are designed to provide minimum guidelines for programs, facilities, and individuals performing cell transplantation and therapy or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a program, facility, or individual should implement if the standard of practice in the community or applicable governmental laws or regulations establish additional requirements. Each program, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with these Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations.

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INTRODUCTION

The major objective of the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration* (the Standards) is to promote quality medical and laboratory practice in hematopoietic progenitor cell transplantation and other therapies using cellular products. These Standards apply to hematopoietic progenitor cells, defined as self-renewing and/or multi-potent stem cells capable of maturation into any of the hematopoietic lineages, lineage-restricted pluri-potent progenitor cells, and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source). These Standards also include therapeutic cells, defined as nucleated cells from any tissue source (marrow, peripheral blood, umbilical cord, and placental blood) collected for therapeutic use other than as hematopoietic progenitor cells. These Standards apply to all phases of collection, processing, storage, and administration of these cells that have been derived from marrow or peripheral blood, including various manipulations such as removal or enrichment of various cell populations, expansion of hematopoietic cell populations, and cryopreservation.

For hematopoietic progenitor cells or therapeutic cells derived from umbilical cord and/or placental blood, these Standards apply only to the administration of the cellular therapy product, applying the clinical standards for transplantation and the processing standards for preparation for transplantation as appropriate. The fifth edition of these Standards includes requirements for preparing cellular therapy products obtained from cord blood banks and/or registries. These standards were added in response to documented adverse reactions and theoretical risks regarding the processing and use of cord blood units by clinical programs and processing facilities either unfamiliar with such products or lacking the appropriate processes, supplies, reagents, equipment, and/or storage space. These Standards do not apply to the collection, processing, or banking of umbilical cord and placental blood cells. Standards for these processes are found in the *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration*.

The FACT-JACIE Standards also do not address the collection, processing, or administration of erythrocytes, platelets, mature granulocytes, plasma, or plasma-derived products intended for transfusion support.

Every effort has been made in these Standards to incorporate sound recommendations fostering quality medical and laboratory practice in cellular therapy. However, no standards can guarantee the successful outcome of such therapies. FACT-JACIE Standards are minimal performance guidelines that may be exceeded as deemed appropriate by the responsible personnel in individual facilities. Directors and Medical Directors of the Clinical Program, Marrow Collection Facility, Apheresis Collection Facility, and Processing Facility assume responsibility for adopting FACT-JACIE Standards as appropriate to the program or facility, and for setting more rigorous internal requirements where appropriate. Attempts have been made to conform these Standards to existing U.S. federal regulations and the requirements of the European Union Directives; however, compliance with these Standards does not guarantee compliance with all regulations. In all cases, personnel must follow all applicable laws and regulations.

The FACT-JACIE Standards are published under the title *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration*, which accurately reflects the contributions of the representatives from both organizations. The Foundation for the Accreditation of Cellular Therapy (FACT) was founded in 1996 by the American Society for Blood and Marrow Transplantation (ASBMT) and the International Society for Cellular Therapy

(ISCT). The first edition of Standards was published that same year. The Inspection and Accreditation Program based on these Standards was started in North America in 1997. The Joint Accreditation Committee of ISCT and EBMT (JACIE) was established in 1999. JACIE adopted the first edition of FACT Standards in its entirety. The second edition of FACT Standards was developed and published in 2002 following joint review by FACT and JACIE. Since that time, the Standards are developed entirely by joint working groups, with representation from both FACT and JACIE. Final documents are approved by both Boards of Directors.

The Standards are structured to align similar standards among the three primary functions within a cellular therapy program: the Clinical Program, Collection Facility, and Processing Facility. In this edition, separate sections exist for Marrow Collection Facilities and Apheresis Collection Facilities to recognize the inherent differences between these two facilities and the closer linkage between the Marrow Collection Facility and the Clinical Program so as to reduce unnecessary overlap. Similar standards were kept consistent across all sections wherever appropriate.

The Quality Management (QM) section for each area in the transplant program was expanded in the third edition (2006), with specific requirements detailed. Standards were added to incorporate the new regulatory requirements for donor screening, testing, and eligibility determination, labeling, and current Good Tissue Practices as published by the U.S. FDA. In the fourth edition, the QM standards were realigned to reduce redundant references to QM topics, yet still maintain the rigorous assurances of a QM Program that results in high-quality cellular therapy. Some redundancies remain in order to allow flexibility with how a cellular therapy program chooses to operate its QM activities among clinical, collection, and processing. Because the clinical team often plays a major role in the activities of Marrow Collection Facilities, the QM requirements in Part B Clinical Program Standards apply to Marrow Collection Facilities. Facilities operating independently of a Clinical Program must still submit documentation of compliance with the QM section in Part B.

Appendices are used to clarify requirements and simplify the Standards. FACT-JACIE Standards require compliance with the most recent regulatory requirements and the most current resources from some industry initiatives. For this reason, the fourth edition included an appendix listing website addresses to external information so that the information required by the Appendices was the most recent. This includes the Transplant Essential Data (TED) forms, the Minimum Essential Data – Form A (MED-A) forms, the Circular of Information (COI) donor testing and biohazard and warning label tables, and the *ISBT 128* Standard Terminology. In the fifth edition, this appendix was removed and the specific titles of the external resources were included in the actual standards. Links to these resources can be found on the FACT website, enabling a listing of current versions and website addresses.

The Donor Selection, Evaluation, and Management sections in the Clinical Program and Collection Facility sections reflect the usual delineation of such responsibilities between clinical programs and collection facilities. The Collection Facility standards focus more on donor evaluation and management, with less emphasis on donor selection activities. To account for situations in which the Collection Facility is primarily responsible for donor selection activities, standards were included to establish that the Collection Facility in those situations are required to comply with the applicable Clinical Program standards. The Donor Selection, Evaluation, and Management sections apply to both related and unrelated donors. Effort was made to clarify when standards apply to both allogeneic and autologous transplantation and when standards apply to allogeneic transplantation only.

Both FACT and JACIE recognize the significant benefits of international standardization of coding and labeling in cellular therapy, and support the international efforts to implement *ISBT 128*, the international information standard for transfusion and transplantation. These FACT-JACIE Standards require the use of this terminology for hematopoietic progenitor cell and therapeutic products as applicable. In the fifth edition, cellular therapy programs are required to create a plan for fully implementing *ISBT 128* technology. At an early stage in the implementation plan for introducing bar coding or other machine readable technology, the Clinical Program, Collection Facility, and/or Processing Facility as appropriate, should register with ICCBBA, Inc., the organization charged with the international maintenance of this database, in order to obtain the necessary documents and databases.

These Standards are effective May 31, 2012. All accredited programs and facilities are expected to be in compliance with these Standards by that date.

ACCREDITATION

The basis for FACT or JACIE Accreditation is documented compliance with the current edition of these Standards. Although there are joint FACT-JACIE Standards, FACT and JACIE maintain separate and parallel accreditation processes. Accreditation is determined by evaluation of the written information provided by the applicant facility and by on-site inspection. All inspections are conducted by persons qualified by training and experience in cellular therapy who are affiliated with an accredited or applicant facility, have completed inspector training, and who have a working knowledge of FACT-JACIE Standards and of their application to various aspects of the cellular therapy program.

1) A clinical hematopoietic progenitor cell/therapeutic cell transplantation program may apply for accreditation alone or in conjunction with the collection facility and/or the processing facility with which it is associated. All facilities applying together should submit pre-inspection data together. If applying separately, a clinical program must use a collection facility and a processing facility that meet FACT-JACIE Standards and have a clearly defined contractual or reporting relationship.

2) A cell collection facility or service (peripheral blood or bone marrow) may apply for accreditation as an integral part of a clinical transplant program, as a local or regional collection service providing cell collection services for one or more clinical transplant programs, or in conjunction with a cell processing facility if the services of collection and processing/storage are functionally linked. An accredited cell collection facility may provide services for clinical transplant programs that are or are not FACT or JACIE accredited, but shall use a processing facility that meets FACT-JACIE Standards.

3) A cell processing facility may apply for accreditation as an integral part of a clinical transplant program, as part of a collection service or facility, or as an independent facility that processes and stores products for clinical program(s) or collection facilities. An accredited processing facility may provide services for clinical transplant programs and/or collection services that are or are not FACT or JACIE accredited.

Accreditation of the Clinical Program may be for allogeneic transplantation, autologous transplantation, or both. The accreditation may cover cells derived from bone marrow and/or peripheral blood. Transplantation of umbilical cord and/or placental blood is included in allogeneic or autologous transplantation standards, as appropriate. Additionally, accreditation of the Clinical Program may be for transplantation of adult patients, pediatric patients, or both. As detailed in the Standards, consultants and support services appropriate to the patient population are required.

An accreditation cycle for FACT is three years, and is four years for JACIE. Accredited facilities must complete an interim report(s) during the accreditation cycle as directed by FACT or JACIE. Accredited facilities are reinspected routinely every three years (FACT) or four years (JACIE), and may also be reinspected in response to complaints or information that a facility may be non-compliant with FACT-JACIE Standards, in response to significant changes in the program and/or facility, or as determined by the FACT or JACIE Board of Directors. Accreditation may be suspended or terminated if a facility fails to comply with the Standards.

Accreditation for the collection and/or banking of cord blood cells is offered to facilities demonstrating compliance with the current edition of the *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration*. There is a separate application and inspection process for NetCord-FACT accreditation. NetCord-FACT Standards do not cover the clinical transplantation of umbilical cord and placental blood cells.

PART A: TERMINOLOGY, ABBREVIATIONS, AND DEFINITIONS

A1 Terminology

A2 Abbreviations

A3 Definitions

PART A: TERMINOLOGY, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

For purposes of these Standards, the term *shall* means that the standard is to be complied with at all times. The term *should* indicates an activity that is recommended or advised, but for which there may be effective alternatives. The term *may* is permissive and is used primarily for clarity.

A2 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

Abbreviations

ABO	Major human blood group including erythrocyte antigens, A, B, O
AC	Accompany
AF	Affixed
Anti-	Antibody to the antigen designated
ASBMT	American Society for Blood and Marrow Transplantation
ASHI	American Society for Histocompatibility and Immunogenetics
AT	Attached
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
cGTP	current Good Tissue Practices
CIBMTR	Center for International Blood and Marrow Transplant Research
CME	Continuing Medical Education
CMS	Centers for Medicare and Medicaid Services
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
CPD	Continuing Professional Development
CTP	Cellular therapy product
DNA	Deoxyribonucleic acid
EBMT	European Group for Blood and Marrow Transplantation
ECP	Extracorporeal photopheresis
EFI	European Federation for Immunogenetics
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	U. S. Food and Drug Administration
HCT/Ps	Human cells, tissues, or cellular or tissue-based products
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cells
IDE	Investigational device exemption
IND	Investigational new drug
ISCT	International Society for Cellular Therapy
JACIE	Joint Accreditation Committee – ISCT and EBMT
OSHA	Occupational Safety and Health Administration
NMDP	National Marrow Donor Program
QM	Quality management
RBC	Red blood cell
Rh	Rhesus systems of human red cell antigens; used in this document to refer to the Rh(D) antigen only, unless otherwise specified
SCTOD	Stem Cell Therapeutics Outcomes Database
SOP	Standard operating procedures

TC	Therapeutic cells
US	United States
USDA	United States Department of Agriculture
WMDA	World Marrow Donor Association

A3 DEFINITIONS

The definitions in this section are descriptive only. In the event of a conflict with the Standards, the Standards shall prevail.

Accompany: To go, be together with, or be available to the appropriate individual(s) electronically, but not affixed or attached. Written or printed information that must accompany a cellular therapy product must be in a sealed package with, or alternatively, be attached or affixed to, the cellular therapy product container.

Accreditation cycle: The period of time from the awarding of accreditation until its expiration as set, and subject to change, by FACT or JACIE. At publication of these Standards, this period is three (3) years for FACT-accredited programs and four (4) years for JACIE-accredited programs.

Advanced Practitioner: Advanced Practitioner of Nursing; includes certified nurse anesthetist, nurse practitioner, certified nurse midwife, and clinical nurse specialist.

Adverse event: Any unintended or unfavorable sign, symptom, abnormality, or condition temporally associated with an intervention that may or may not have a causal relationship with the intervention, medical treatment, or procedure. Adverse reaction is a type of adverse event.

Adverse reaction: A noxious and unintended response suspected or demonstrated to be caused by the collection or infusion of a cellular therapy product or by the product itself.

Affix: To adhere in physical contact with the cellular therapy product container.

Allogeneic: The biologic relationship between genetically distinct individuals of the same species.

Apheresis: A medical technology in which the blood of a donor is separated into its component parts, the desired component is removed, and the remaining components are returned to the donor.

Aseptic technique: Practices designed to reduce the risk of microbial contamination of cellular therapy products, reagents, specimens, recipients, and/or donors.

Attach: To fasten securely to the cellular therapy product container by means of a tie tag or comparable alternative. Any information required to be attached to a cellular therapy product container may alternatively be affixed.

Audit: Documented, systematic evaluation to determine whether approved policies or procedures have been properly implemented and are being followed.

Autologous: Derived from and intended for the same individual.

Available for distribution: The time at which the cellular therapy product may leave the control of the facility.

Biological product deviation: Any event associated with the manufacturing of a cellular therapy product, including testing, processing, packing, labeling, or storage, or with the holding or distribution, of a licensed biological product, if that event meets the following criteria: Either:

- Represents a deviation from current good manufacturing practice (or current good tissue practices), applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or
- Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and
  - Occurs in your facility or another facility under contract with you; and
  - Involves a distributed biological product.

Calibrate: To set measurement equipment against a known standard.

CD34: The 115 kD glycoprotein antigen, expressed by 1-2% of normal bone marrow mononuclear cells, that is defined by a specific monoclonal antibody (anti-CD34) using the standardized cluster of differentiation (CD) terminology.

Cellular therapy: The administration of products with the intent of providing effector cells in the treatment of disease or support of other therapy.

Cellular therapy product: Somatic cell-based product (e.g. mobilized HPC, therapeutic cells, cord blood cells, mesenchymal stromal cells) that is procured from a donor and intended for processing and administration.

Circular of information: An extension of container labels that includes the use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

Clinical Program: An integrated medical team housed in geographically contiguous or proximate space with a single Clinical Program Director and common staff training programs, protocols, and quality management systems. The Clinical Program shall use cell collection and processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Clinical Program. Clinical Programs that include non-contiguous institutions shall demonstrate evidence of regular interaction and common protocols, staff training procedures, quality management systems, and review of clinical results.

Collection: Any procedure for procuring and labeling a cellular therapy product regardless of technique or source.

Collection Facility: An entity providing the service of cellular therapy product collection. A Collection Facility may be part of the same institution as the Clinical Program or may be part of another institution and perform cellular therapy product collection services through contractual agreement.

Competency: Ability to adequately perform a specific procedure or task according to direction.

Complaint: Any written, oral, or electronic communication about a problem associated with a cellular therapy product or with a service related to the collection, processing, storage, distribution, or administration of a cellular therapy product.

Cord blood: The whole blood, including HPC, collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped.

Corrective action: Action taken to eliminate the causes of an existing discrepancy or other undesirable situation to prevent recurrence.

Critical: The quality of any element employed in cellular therapy product manufacturing to potentially change the identity, purity, potency, or safety of the cellular therapy product if altered or omitted. "Element" includes, but is not limited to, materials, equipment, personnel, documents, or facility. For example, DMSO is a critical reagent because omitting it from the freezing medium will cause loss of cells during freezing and thawing.

Current Good Tissue Practice: The methods used in, and the facilities and controls used for, the manufacture of cellular therapy products to prevent the introduction or transmission of communicable diseases, including all steps in collection, donor screening and testing, processing, storage, labeling, packaging, and distribution.

Current Good Manufacturing Practice: The set of current practices followed by entities producing drug and biologic products, including cellular therapy products, to ensure that the products produced meet specific requirements for identity, strength, quality, and purity. In the US, cGMPs are enforced under Section 501(B) of the Federal Food, Drug, and Cosmetic Act (21USC351). Cellular therapy products that are extensively manipulated or that are used for non-autologous purposes are controlled under cGMP regulations. Similar requirements are enforced by the European Union as EU-GMP, and other countries such as United Kingdom, Australia, Canada, and Singapore have equally well-developed systems of regulations.

Designee: An individual with appropriate education, experience, or expertise who is given the authority to assume a specific responsibility. The person appointing the designee retains ultimate responsibility.

Deviation: The action of departing from an established course or accepted standard.

Unplanned Deviation: Occurred without intent.

Planned Deviation: Was allowed to occur with documented approval as the best course of action when adherence to the established course or accepted standard was not feasible or possible.

Distribution: Any transportation or shipment of a cellular therapy product that has been determined to meet release criteria or urgent medical need requirements.

Donor: A person who is the source of cells or tissue for a cellular therapy product.

Donor advocate: An individual distinct from the transplant recipient's primary treating physician whose primary obligation is to help the donor understand the process, the procedures, and the risks and benefits of donation. The advocate should protect and promote the interests, well-being, and safety of the donor.

Electronic record: A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer.

Eligible: An allogeneic cellular therapy product donor who meets all donor screening and testing requirements related to transmission of infectious disease as defined by applicable laws and regulations.

Engraftment: The reconstitution of recipient hematopoiesis with blood cells and platelets from a donor.

Errors and Accidents: Any unforeseen or unexpected deviations from applicable regulations, standards, or established specifications that may affect the safety, purity, or potency of a cellular therapy product.

Establish and maintain: A process to define, document in writing (including electronically), implement, follow, review, and, as needed, revise on an ongoing basis.

Exceptional release: Removal of a product that fails to meet specified criteria from quarantine or in-process status for distribution. Requires documented approval.

Expansion: Growth of one or more cell populations in an *in vitro* culture system.

Extracorporeal photopheresis: An apheresis technique in which the patient's blood is collected into a specialized instrument, centrifuged, and separated into a leukocyte-depleted fraction (which is returned to the patient unmanipulated) and mononuclear "buffy coat" enriched plasma. The mononuclear cell-enriched fraction is incubated with 8-methoxypsoralen in the presence of ultraviolet A (UVA) radiation, and, upon completion of the procedure, reinfused into the patient.

Facility: A location where activities covered by these Standards are performed. Such activities include determination of donor eligibility or suitability, product collection, processing, storage, distribution, issue, and administration.

Fresh: A cellular therapy product that has never been cryopreserved.

Hematopoietic progenitor cells (HPC): A cellular therapy product that contains self-renewing and/or multi-potent stem cells capable of maturation into any of the hematopoietic lineages, lineage-restricted pluri-potent progenitor cells, and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source).

Hematopoietic progenitor cellular therapy: The infusion of HPC product with the intent of providing effector functions in the treatment of disease or in support of other therapy.

Human cells, tissues, or cellular or tissue-based products (HCT/Ps): Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

Ineligible: An allogeneic cellular therapy product donor who does not meet all donor screening and testing requirements related to transmission of infectious disease as defined by applicable laws and regulations.

Institutional Review Board or Ethics Committee: A Board or Committee established by an institution in accordance with the regulations of the relevant governmental agency to review biomedical and behavioral research that involves human subjects and is conducted at or supported by that institution.

**ISBT 128*: The international information technology standard for transfusion medicine and transplantation.

Key position: A job category with responsibilities that significantly affect the provision of service or product safety and quality.

Labeling: Steps taken to identify the original cellular therapy product collection and any products or product modifications, to complete the required reviews, and to attach the appropriate labels.

Licensed health care professional: An individual who has completed a prescribed program of health-care related study and has been certified or licensed by the applicable authority in the jurisdiction in which he or she is performing services to perform duties within the scope of practice of that certificate or license.

Manipulation: An ex vivo procedure(s) that selectively removes, enriches, expands, or functionally alters HPC products.

Minimally Manipulated: Processing that does not alter the relevant biological characteristics of cells or tissues.

More than minimally manipulated: Processing that does alter the relevant biological characteristics of cells or tissues.

Unmanipulated hematopoietic progenitor cells: HPC as obtained at collection and not subjected to any form of processing.

Manufacturing: Includes, but is not limited to, any or all steps in the recovery, processing, packaging, labeling, storage, or distribution of any human cellular or tissue-based product, and the screening and testing of a cell or tissue donor.

Materials management: An integrated process for planning and controlling all steps in the acquisition and use of goods or supply items (materials) used for the collection or processing of cellular therapy products to determine whether these materials are of adequate quality and quantity and available when needed. The materials management system combines and integrates the material selection, vendor evaluation, purchasing, expediting, storage, distribution, and disposition of materials.

Microbial: Related to infectious agents including bacterial and fungal organisms.

Mid-Level Practitioner: Physician Assistant, Nurse Practitioner, or other Advanced Practitioner who provides primary patient care with physician oversight.

Negative selection: The manipulation of a cellular therapy product such that a specific cell population(s) is reduced.

Nurse Practitioner: A nurse with a graduate degree in advanced practice nursing who is licensed or certified by the applicable authority to provide patient services in defined areas of practice in collaboration with other health professionals.

New patient: An individual undergoing the specified type of transplantation (allogeneic, autologous, or syngeneic) for the first time in the Clinical Program whether or not that patient was previously treated by that Clinical Program.

Orientation: An introduction to guide a new employee in adjusting to new surroundings, employment, activity, or similar.

Outcome analysis: The process by which the results of a therapeutic procedure are formally assessed.

Partial label: The minimum essential elements that must be affixed to all cellular therapy product containers at all times.

Physician Assistant: A person formally trained and licensed or certified by the applicable authority to provide diagnostic, therapeutic, and preventive health care services with physician supervision.

Policy: A document that defines the scope of an organization, explains how the goals of the organization will be achieved, and/or serves as a means by which authority can be delegated.

Positive selection: The manipulation of a cellular therapy product such that a specific cell population(s) is enriched.

Potency: The therapeutic activity of a product as indicated by appropriate laboratory tests or adequately developed and controlled clinical data.

Preventive action: Action taken to eliminate the cause and prevent occurrence of a potential discrepancy or other undesirable situation.

Procedure: A document that describes in detail the process or chronological steps taken to accomplish a specific task; a procedure is more specific than a policy.

Process: A goal-directed, interrelated series of actions, events, or steps.

Process control: The standardization of processes in order to produce predictable output.

Process development: The series of procedures performed in order to develop a final process that achieves the required results.

Processing: All aspects of manipulation, cryopreservation, packaging, and labeling of cellular therapy products regardless of source, including microbial testing, preparation for administration or storage, and removal from storage. Processing does not include collection, donor screening, donor testing, storage, or distribution.

Processing Facility: A location where cellular therapy product processing activities are performed in support of the Clinical Program. A Processing Facility may be part of the same institution as the Clinical Program or may be part of another institution and perform these functions through contractual agreement.

Product sample: A representative quantity of product removed from the cellular therapy product; an aliquot.

**Products*: The proper name for each class (broad descriptions of products*)* is as follows:

Concurrent Plasma, Apheresis: Plasma collected from the donor as part of an apheresis cell collection procedure for use by the laboratory in further processing of that donor's product.

HPC, Apheresis: Peripheral blood collected by apheresis as a source of hematopoietic progenitor cells. Mobilized unless otherwise stated in modifier.

HPC, Cord Blood: Umbilical cord blood and/or placental blood collected as a source of hematopoietic progenitor cells.

HPC, Marrow: Bone marrow collected as a source of hematopoietic progenitor cells.

HPC, Whole Blood: Whole blood collected as a source of hematopoietic progenitor cells. Mobilized unless otherwise stated in modifier.

TC, Apheresis: Source of nucleated cells obtained by an apheresis procedure intended for therapeutic use other than HPCs. Non-mobilized unless otherwise stated in the modifier.

TC, Cord Blood: Umbilical cord blood and/or placental blood collected as a source of nucleated cells intended for therapeutic use other than HPCs.

TC, Marrow: Bone marrow collected as a source of nucleated cells intended for therapeutic use other than HPCs.

TC, Tumor Derived: A product containing malignant cells or elements derived from them.

TC, Whole Blood: Whole blood collected as a source of nucleated cells intended for therapeutic use other than HPCs.

TC-APC: A therapeutic cell product containing antigen presenting cells other than dendritic cells for therapeutic use.

TC-Blinded Study: This class is reserved for use only in blinded studies of therapeutic cells that is accompanied by appropriate identifying study information. Products labeled as TC-Blinded Study may include different doses or may include an active product and a placebo.

TC-CTL: A therapeutic cell product containing cytotoxic lymphocytes for therapeutic use.

TC-DC: A therapeutic cell product containing dendritic cells for therapeutic use.

TC-INV: Therapeutic cell product for an investigational study that is accompanied by appropriate identifying study information. This class is used for a specific product, not a product that is part of a blinded comparison study. Throughout the study, products labeled as TC-INV will be the same product, although the dose may vary within a specified range defined by the study.

TC-MSC: A therapeutic cell product containing mesenchymal stromal cells for therapeutic use.

TC-NK cells: A therapeutic cell product containing natural killer cells for therapeutic use.

TC-T Cells: A therapeutic cell product from any source containing a quantified T cell population.

TC-T Reg Cells: A therapeutic cell product containing T regulatory lymphocytes for therapeutic use.

Proficiency test: A test to evaluate the adequacy of testing methods and equipment and the competency of personnel performing testing.

Protocol: A written document describing steps of a treatment or procedure in sufficient detail such that the treatment or procedure can be reproduced repeatedly without variation.

Purity: Relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.

Qualification: The establishment of confidence that equipment, supplies, and reagents function consistently within established limits.

Quality: Conformance of a product or process with pre-established specifications or standards.

Quality assurance: The actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected individually and collectively.

Quality assessment: The actions, planned and performed, to evaluate all systems and elements that influence the quality of the product or service.

Quality audit: A documented, independent inspection and review of a facility's quality management activities to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

Quality control: A component of a quality management program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of cellular therapy products, including testing and product release.

Quality handbook: A document describing the application of general principles of quality management in cellular therapy programs using templates, scenarios, and sample documentation. It is an adjunct to help cellular therapy programs prepare for and maintain FACT or JACIE accreditation. May also be referred to as a quality guide or manual.

Quality improvement: The actions, planned and performed, to implement changes designed to improve the quality of a product or process.

Quality management: An integrated program of quality assessment, assurance, control, and improvement.

Quality management plan: A written document that describes the systems in place to implement the quality management program. May also be referred to as the quality management manual or handbook.

Quality management program: An organization's comprehensive system of quality assessment, assurance, control, and improvement. A quality management program is designed to prevent, detect, and correct deficiencies that may adversely affect the quality of the cellular therapy product or increase the risk of communicable disease introduction or transmission. May also be referred to as the quality management system.

Quarantine: The identification or storage of a cellular therapy product in a physically separate area clearly identified for such use, or through use of other procedures such as automated designation to prevent improper release of that product. Also refers to segregated storage of products known to contain infectious disease agents to reduce the likelihood of cross-contamination.

Record: Documented evidence that activities have been performed or results have been achieved. A record does not exist until the activity has been performed.

Release: Removal of a product from quarantine or in-process status when it meets specified criteria.

Release criteria: The requirements that must have been met before a cellular therapy product may leave the control of the Collection or Processing Facility.

Responsible person: A person who is authorized to perform designated functions for which he or she is trained and qualified.

Safety: Relative freedom from harmful effects to persons or products.

Shipping: The physical act of transferring a cellular therapy product within or between facilities. During shipping the product leaves the control of trained personnel at the distributing or receiving facility.

Standard Operating Procedures (SOP) Manual: A compilation of policies and procedures with written detailed instructions required to perform procedures. The SOP Manual may be in electronic or paper format.

Standards: The current edition of the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration*, which may be referred to herein as "Standards" or "FACT-JACIE Standards."

Storage: Holding a cellular therapy product for future processing, distribution, or administration.

Syngeneic: The biologic relationship between identical twins.

Therapeutic cells: Nucleated cells from any source (marrow, peripheral blood, or umbilical cord and/or placental blood) intended for therapeutic use other than as HPC.

Time of collection: The time of day at the end of the cellular therapy product collection procedure.

Trace: To follow the history of a process, product, or service by review of documents.

Track: To follow a process or product from beginning to end.

Transplantation: The infusion of allogeneic, autologous, or syngeneic HPC with the intent of providing transient or permanent engraftment in support of therapy of disease.

Transport: The physical act of transferring a cellular therapy product within or between facilities. During transportation the product does not leave the control of trained personnel at the transporting or receiving facility.

Unique: Being the only one of its kind or having only one use or purpose.

Unique identifier: A numeric or alphanumeric sequence used to designate a given cellular therapy product with reasonable confidence that it will not be used for another purpose.

Urgent medical need: A situation in which no comparable cellular therapy product is available and the recipient is likely to suffer death or serious morbidity without the cellular therapy product.

Validation: Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process is validated by establishing, by objective evidence, that the process consistently produces a cellular therapy product meeting its predetermined specifications.

Variance: A planned deviation from recommended practice or standard operating procedure.

Verification: The confirmation of the accuracy of something or that specified requirements have been fulfilled.

Verification typing: HLA typing performed on an independent sample with the purpose of verifying concordance of that typing assignment with the initial HLA typing assignment. Concordance does not require identical levels of resolution for the two sets of typing but requires the two assignments be consistent with one another.

Viability: Living cells as defined by dye exclusion, flow cytometry, or progenitor cell culture.

Written: Documentation in human readable form.

**These definitions are as of publication and use the current terminology as found in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.*

PART B: CLINICAL PROGRAM STANDARDS

B1 General

B2 Clinical Unit

B3 Personnel

B4 Quality Management

B5 Policies and Procedures

B6 Allogeneic and Autologous Donor Selection, Evaluation, and Management

B7 Therapy Administration

B8 Clinical Research

B9 Data Management

B10 Records

PART B: CLINICAL PROGRAM STANDARDS

B1 GENERAL

B1.1 The Clinical Program consists of an integrated medical team housed in geographically contiguous or proximate space with a Clinical Program Director(s) and common staff training, programs, protocols, and quality management systems.

B1.1.1 Clinical Programs that include non-contiguous institutions shall demonstrate common protocols, procedures, quality management systems, and review of clinical results and evidence of regular interaction.

B1.2 The Clinical Program shall use cell collection and processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Clinical Program.

B1.3 The Clinical Program shall abide by all applicable laws and regulations.

B1.3.1 The Clinical Program shall be licensed, registered, and/or accredited as required by the appropriate governmental authorities for the activities performed.

B1.4 For initial accreditation, a dedicated transplant team including a Clinical Program Director(s) and at least one other physician trained and/or experienced in cellular therapy and/or HPC transplantation shall have been in place for at least twelve (12) months preceding accreditation.

B1.5 If the Clinical Program requests accreditation for allogeneic HPC transplantation, a minimum of ten (10) new allogeneic patients shall have been transplanted during the twelve (12) month period immediately preceding program accreditation and a minimum average of ten (10) new allogeneic patients shall be transplanted per year within the accreditation cycle. A Clinical Program that is accredited for allogeneic transplantation will be considered to have met the numeric requirement for autologous transplantation.

B1.5.1 For Clinical Programs utilizing more than one clinical site and requesting accreditation for allogeneic HPC transplantation, a minimum of five (5) new allogeneic patients shall have been transplanted at each site performing allogeneic transplants during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new allogeneic patients shall be transplanted at each site performing allogeneic transplants per year within the accreditation cycle. A site that is accredited for allogeneic transplantation will be considered to have met the numeric requirement for autologous transplantation.

B1.5.1.1 For clinical sites performing only autologous transplants, a minimum of five (5) new autologous patients shall have been transplanted at each site during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new autologous patients shall be transplanted at each site per year within the accreditation cycle.

B1.5.2 A combined Clinical Program caring for pediatric and adult patients at the same site shall perform a minimum average of five (5) allogeneic HPC transplants for each population per year within the accreditation cycle.

B1.6 If the Clinical Program requests accreditation for only autologous HPC transplantation, a minimum of five (5) new recipients of autologous transplantation shall have been transplanted during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new recipients of autologous transplantation shall be transplanted per year within the accreditation cycle.

B1.6.1 For Clinical Programs utilizing more than one clinical site and requesting accreditation for autologous HPC transplantation only, a minimum of five (5) new patients shall have been transplanted at each site during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new patients shall be transplanted at each site per year within the accreditation cycle.

B1.6.2 A combined Clinical Program requesting accreditation for autologous HPC transplantation only and caring for pediatric and adult patients at the same site shall perform a minimum average of five (5) transplants for each population per year within the accreditation cycle.

B2 CLINICAL UNIT

B2.1 There shall be a designated inpatient unit of adequate space, design, and location that minimizes airborne microbial contamination.

B2.1.1 The inpatient program shall have an intensive care unit or equivalent coverage available.

B2.1.1.1 There shall be written guidelines for clear communication and prompt transfer during and ongoing monitoring of the transfer of patients to an intensive care unit or equivalent coverage.

B2.2 There shall be a designated area for outpatient care that protects the patient from transmission of infectious agents and allows, as necessary, for appropriate patient isolation; administration of intravenous fluids, medications, and/or blood products; and confidential donor examination and evaluation.

B2.2.1 Outpatient facilities shall have a plan for providing access to an intensive care unit or equivalent coverage for patients who may become critically ill.

B2.3 Facilities used by the Clinical Program shall be maintained in a clean, sanitary, and orderly manner.

B2.4 The following shall apply to both inpatient and outpatient care:

B2.4.1 There shall be provisions for prompt evaluation and treatment by a transplant attending physician available on a 24-hour basis.

B2.4.1.1 If general medical physicians provide inpatient-based care to transplant patients, there shall be a policy for their scope of care and afterhours coverage.

B2.4.2 There shall be a pharmacy providing 24-hour availability of medications needed for the care of transplant patients.

B2.4.3 There shall be access to renal support under the direction of nephrologists and trained personnel.

B2.4.4 There shall be 24-hour availability of autologous and/or CMV-appropriate and irradiated blood products needed for the care of transplant patients.

B2.4.5 The Clinical Program shall refer planned discharges to facilities and health care professionals adequate for post-transplant care.

B2.4.5.1 The Clinical Program shall provide or secure oversight of care that meets applicable standards.

B2.4.6 Clinical Programs performing allogeneic cell transplants shall use HLA testing laboratories appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), or equivalent, with the capability of carrying out deoxyribonucleic acid (DNA)–based HLA-typing.

B2.5 SAFETY REQUIREMENTS

B2.5.1 The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.

B2.5.2 The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

B3 PERSONNEL

B3.1 CLINICAL PROGRAM DIRECTOR

B3.1.1 The Clinical Program Director shall be a physician appropriately licensed or certified to practice medicine in the jurisdiction in which the program is located who has achieved specialist certification in one or more of the following specialties: Hematology, Medical Oncology, Pediatric Immunology, or Pediatric Hematology/Oncology. Physicians trained prior to requirements for specialty training may serve as Clinical Program Director if they have documented experience in the field of HPC transplantation extending over ten (10) years.

B3.1.2 The Clinical Program Director shall have two (2) years of experience as an attending physician responsible for the direct clinical management of HPC transplant patients in the inpatient and outpatient settings.

B3.1.3 The Clinical Program Director shall be responsible for administrative and clinical operations, including compliance with these Standards and applicable laws and regulations.

B3.1.4 The Clinical Program Director shall be responsible for all elements of the design of the Clinical Program including quality management, the selection and care of patients and donors, cell collection, and processing, whether internal or contracted services.

B3.1.5 The Clinical Program Director shall have oversight of the medical care provided by all members of the Clinical Program including medical care provided by the physicians on the transplant team.

B3.1.5.1 The Clinical Program Director shall be responsible for verifying the knowledge and skills of the physicians and mid-level practitioners of the transplant team.

B3.1.6 The Clinical Program Director shall participate regularly in educational activities related to the field of HPC transplantation.

B3.2 ATTENDING PHYSICIANS

B3.2.1 Clinical Program attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program and should be specialist certified or trained in one of the following specialties: Hematology, Medical Oncology, Adult or Pediatric Immunology, or Pediatric Hematology/Oncology.

B3.2.2 Clinical Program attending physicians shall participate regularly in educational activities related to the field of HPC transplantation.

B3.3 CLINICAL TRANSPLANT TEAM

B3.3.1 Clinical Programs performing pediatric transplantation shall have a transplant team trained in the management of pediatric patients.

B3.3.2 Clinical Programs performing pediatric transplantation shall have at least one attending physician who has achieved specialist certification in Pediatric Hematology or Oncology or Pediatric Immunology. An attending physician may also serve as the Clinical Program Director, if appropriately credentialed.

B3.3.3 For Clinical Programs performing adult transplantation, there shall be at least one attending physician who has achieved specialist certification in Hematology, Medical Oncology, or Immunology. An attending physician may also serve as the Clinical Program Director, if appropriately credentialed.

B3.3.4 The Clinical Program shall have access to licensed physicians who are trained and competent in marrow collection and a marrow collection facility that meets these Standards.

B3.3.5 The Clinical Program shall have access to personnel who are trained and competent in cellular therapy product collection by apheresis and an apheresis collection facility that meets these Standards.

B3.4 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.4.1 Attending physicians shall each have a total of one year of supervised training in the management of transplant patients in both inpatient and outpatient settings.

B3.4.2 Clinical training and competency shall include the management of:

B3.4.2.1 Autologous transplant patients for physicians in Clinical Programs requesting accreditation for autologous transplantation.

B3.4.2.2 Allogeneic transplant patients for physicians in Clinical Programs requesting accreditation for allogeneic transplantation.

B3.4.2.3 Both allogeneic and autologous transplant patients for physicians in Clinical Programs requesting accreditation for allogeneic and autologous transplantation.

B3.4.3 Clinical Program Directors and attending physicians in all Clinical Programs shall have received specific training and maintain competency in each of the following areas:

B3.4.3.1 Indications for HPC transplantation.

B3.4.3.2 Selection of appropriate patients and preparative regimens.

B3.4.3.3 Pre-transplant patient evaluation, including assessment of appropriate patient eligibility and HPC adequacy with respect to collection.

B3.4.3.4 Donor and recipient informed consent.

B3.4.3.5 Administration of preparative regimens.

B3.4.3.6 Donor evaluation and management.

B3.4.3.7 Administration of growth factors for HPC mobilization and for post-transplant hematopoietic cell reconstitution.

B3.4.3.8 HPC product infusion and patient management.

B3.4.3.9 Management of neutropenic fever.

B3.4.3.10 Diagnosis and management of infectious and non-infectious pulmonary complications of transplantation.

B3.4.3.11 Diagnosis and management of fungal disease.

B3.4.3.12 Diagnosis and management of veno-occlusive disease of the liver.

B3.4.3.13 Management of thrombocytopenia and bleeding.

B3.4.3.14 Management of hemorrhagic cystitis.

B3.4.3.15 Management of mucositis, nausea, and vomiting.

B3.4.3.16 Management of pain.

B3.4.3.17 Palliative and end of life care.

B3.4.3.18 Diagnosis and management of HPC graft failure.

B3.4.3.19 Evaluation of post-transplant cellular therapy outcomes.

B3.4.3.20 Evaluation of late effects of allogeneic and autologous transplants, including cellular, pharmacologic, and radiation therapy.

B3.4.3.21 Documentation and reporting for patients on investigational protocols.

B3.4.3.22 Applicable regulations and reporting responsibilities for adverse events.

B3.4.4 Additional specific clinical training and competency required for physicians in Clinical Programs requesting accreditation for allogeneic HPC transplantation shall include:

B3.4.4.1 Identification, evaluation, and selection of HPC source, including use of donor registries.

B3.4.4.2 Donor eligibility determination.

B3.4.4.3 Methodology and implications of human leukocyte antigen (HLA) typing.

B3.4.4.4 Management of patients receiving ABO incompatible HPC products.

B3.4.4.5 Diagnosis and management of cytomegalovirus (CMV) infection and disease.

B3.4.4.6 Diagnosis and management of other viral infections in immunocompromised hosts.

B3.4.4.7 Diagnosis and management of acute and chronic graft versus host disease.

B3.4.4.8 Diagnosis and management of post-transplant immunodeficiencies.

B3.4.5 The attending physicians shall be knowledgeable in the following procedures:

B3.4.5.1 HPC processing.

B3.4.5.2 HPC cryopreservation.

B3.4.5.3 Marrow collection procedures.

B3.4.5.4 Apheresis collection procedures.

B3.4.5.5 Extracorporeal photopheresis for allogeneic transplants, if applicable.

B3.5 MID-LEVEL PRACTITIONERS (Physician Assistants, Nurse Practitioners, Advanced Practitioners)

B3.5.1 Mid-level practitioners shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to the scope of practice of their licenses and within parameters of their training.

B3.5.2 Mid-level practitioners shall have received specific training and maintain competency in the transplant-related cognitive and procedural skills that they routinely practice. These skills shall be documented and may include but are not limited to those listed in B3.4.3.

B3.5.3 Mid-level practitioners shall participate regularly in educational activities related to the field of HPC transplantation.

B3.6 NURSES

B3.6.1 The Clinical Program shall have nurses formally trained and experienced in the management of patients receiving cellular therapy.

B3.6.2 A Clinical Program treating pediatric patients shall have nurses formally trained and experienced in the management of pediatric patients receiving cellular therapy.

B3.6.3 Training shall include:

B3.6.3.1 Hematology/oncology patient care, including an overview of the cellular therapy process.

B3.6.3.2 Administration of preparative regimens.

B3.6.3.3 Administration of blood products, growth factors, cellular therapy products, and other supportive therapies.

B3.6.3.4 Care interventions to manage transplant complications, including, but not limited to, neutropenic fever, infectious and

noninfectious processes, mucositis, nausea and vomiting, and pain management.

B3.6.3.5 Recognition of cellular therapy complications and emergencies requiring rapid notification of the clinical transplant team.

B3.6.3.6 Palliative and end of life care.

B3.6.4 There shall be written policies for all relevant nursing procedures, including, but not limited to:

B3.6.4.1 Care of immunocompromised patients.

B3.6.4.2 Administration of preparative regimens.

B3.6.4.3 Administration of cellular therapy products.

B3.6.4.4 Central venous access device care.

B3.6.4.5 Administration of blood products.

B3.6.5 There shall be an adequate number of nurses experienced in the care of transplant patients.

B3.6.6 There shall be a nurse/patient ratio satisfactory to manage the severity of the patients' clinical status.

B3.7 CONSULTING SPECIALISTS

B3.7.1 The Clinical Program shall have access to certified or trained consulting specialists and/or specialist groups from key disciplines who are capable of assisting in the management of patients requiring medical care, including but not limited to:

B3.7.1.1 Surgery.

B3.7.1.2 Pulmonary medicine.

B3.7.1.3 Intensive care.

B3.7.1.4 Gastroenterology.

B3.7.1.5 Nephrology.

B3.7.1.6 Infectious diseases.

B3.7.1.7 Cardiology.

B3.7.1.8 Pathology.

B3.7.1.9 Psychiatry.

B3.7.1.10 Radiology.

B3.7.1.11 Radiation oncology with experience in large-field (e.g., total body or total lymphoid) irradiation treatment protocols, if radiation therapy is administered.

B3.7.1.12 Transfusion medicine.

B3.7.1.13 Neurology.

B3.7.1.14 Palliative and end of life care.

B3.7.2 A Clinical Program treating pediatric patients shall have consultants, as defined in B3.7.1, qualified to manage pediatric patients.

B3.8 QUALITY MANAGEMENT SUPERVISOR

B3.8.1 There should be a Clinical Program Quality Management Supervisor approved by the Program Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Clinical Program.

B3.8.2 The Clinical Program Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular therapy, and/or quality management.

B3.9 SUPPORT SERVICES STAFF

B3.9.1 The Clinical Program shall have one or more designated staff with appropriate training and education to assist in the provision of pre-transplant patient evaluation, treatment, and post-transplant follow-up and care. Designated staff shall include:

B3.9.1.1 Pharmacy staff knowledgeable in the use and monitoring of pharmaceuticals used by the Clinical Program.

B3.9.1.2 Dietary staff capable of providing dietary consultation regarding the nutritional needs of the transplant recipient, including enteral and parenteral support, and appropriate dietary advice to avoid food-borne illness.

B3.9.1.3 Social Services staff.

B3.9.1.4 Psychology Services staff.

B3.9.1.5 Physical Therapy staff.

B3.9.1.6 Data Management staff sufficient to comply with B9.

B4 QUALITY MANAGEMENT

B4.1 There shall be an overall Quality Management Program that incorporates key performance data from clinical, collection, and processing facility quality management.

B4.1.1 The Clinical Program shall establish and maintain a written Quality Management Plan.

B4.2 The Quality Management Plan shall include an organizational chart of key personnel and functions within the cellular therapy program, including clinical, collection, and processing.

B4.2.1 The Quality Management Plan shall include a description of how these key personnel interact to implement the quality management activities.

B4.2.2 The Clinical Program Director or designee shall be responsible for the Quality Management Plan.

B4.2.2.1 The Clinical Program Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

B4.2.2.2 The Clinical Program Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Clinical Program.

B4.2.2.3 The Clinical Program Director or designee shall report on quality management activities, at a minimum, quarterly.

B4.2.2.4 The Clinical Program Director shall report on the performance of the Quality Management Plan, at a minimum, annually.

B4.3 The Quality Management Plan shall include, or summarize and reference, personnel education, experience, and training requirements for each key position in the Clinical Program. Personnel requirements shall include at a minimum:

B4.3.1 A system to document the following for all medical and nursing staff:

B4.3.1.1 Initial qualifications and training.

B4.3.1.2 Competency for each critical function performed.

B4.3.1.3 Continued competency at least annually.

B4.3.1.4 Annual performance review.

B4.3.1.5 Provisions for continuing education.

B4.3.2 A policy and/or procedure for personnel training and competency assessment.

B4.4 The Quality Management Plan shall include, or summarize and reference, policies and procedures for development, approval, implementation, review, revision, and archival of all critical processes, policies, and procedures.

B4.5 The Quality Management Plan shall include, or summarize and reference, a system for document control. The document control system shall include at a minimum the following elements:

B4.5.1 Listing of all active critical documents that shall adhere to the document control system requirements.

B4.5.2 A procedure for preparation, approval, implementation, review, revision, and archival of all policies and procedures.

B4.5.2.1 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

B4.5.3 A standardized format for policies, procedures, worksheets, and forms.

B4.5.4 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.

B4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the clinical care of the patient and/or donor.

B4.6.1 Agreements shall include the responsibility of the third-party facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.

B4.6.2 Agreements shall be dated, reviewed, and renewed on a regular basis.

B4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and product efficacy, as appropriate.

B4.7.1 Review of outcome analysis and product efficacy shall include at a minimum:

B4.7.1.1 For HPC products intended for hematopoietic reconstitution, a process for documentation and review of time to engraftment following product administration.

B4.7.1.2 For HPC products, overall and treatment-related morbidity and mortality at 100 days and 1 year after transplantation.

B4.7.1.3 For other cellular therapy products, the criteria for product efficacy and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

B4.7.2 The Clinical Program shall provide data on outcome analysis and product efficacy, including adverse events related to the patient and/or product, in a timely manner to entities involved in the collection, processing, and/or distribution of the cellular therapy product.

B4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a timetable for conducting, reviewing, and reporting audits of the Clinical Program's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

B4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

B4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, and implement corrective actions when necessary.

B4.8.3 The Clinical Program shall periodically audit at a minimum:

B4.8.3.1 Accuracy of data contained in the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A Forms of the EBMT.

B4.8.3.2 Donor screening and testing.

B4.8.3.3 Verification of chemotherapy drug and dose against the orders and the protocol.

B4.8.3.4 Management of cellular therapy products with positive microbial culture results.

B4.8.4 Collection and analysis of data related to the audit shall be reviewed, reported, and documented, at a minimum, on an annual basis.

B4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

B4.9.1 Notification of the recipient.

B4.9.2 Recipient follow-up and outcome analysis.

B4.9.3 Follow-up of the donor, if relevant.

B4.9.4 Reporting to regulatory agencies if appropriate.

B4.9.5 Criteria for the administration of cellular therapy products with positive microbial culture results.

B4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, adverse events, biological product deviations, and complaints.

B4.10.1 Policies and procedures shall include methods for:

B4.10.1.1 Detection.

B4.10.1.2 Investigation.

B4.10.1.3 Evaluation.

B4.10.1.4 Documentation.

B4.10.1.5 Reporting.

B4.10.1.6 Corrective action.

B4.10.1.7 Follow-up for effectiveness of corrective action.

B4.10.2 Documentation of each adverse event that occurs in the Clinical Program shall be reviewed in a timely manner by the Clinical Program Director.

B4.10.3 A written description of an adverse event shall be made available to the recipient's and/or donor's physician and the Collection and Processing Facilities, if appropriate.

B4.10.4 When applicable, adverse events shall be reported to the appropriate regulatory agencies within the required timeframes.

B4.10.5 Deviations from the following key Standard Operating Procedures, B5.1.1, B5.1.6, and B5.1.7, shall be documented.

B4.10.5.1 Planned deviations shall be pre-approved by the Clinical Program Director or designee.

B4.10.5.2 Unplanned deviations and associated corrective actions shall be reviewed by the Clinical Program Director or designee.

B4.10.6 There shall be a defined process improvement plan that includes policies or procedures for the recognition and investigation of the cause of all issues that require corrective action.

B4.10.6.1 Follow-up activities shall be conducted to determine if the corrective actions were effective.

B4.10.7 There shall be a defined process to obtain feedback from patients and patient representatives.

B4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

B4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Clinical Program's operations are interrupted.

B4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical reagents, supplies, equipment, and facilities used for the marrow collection procedure.

B4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of the marrow collection procedure.

B4.14.1 Changes to the marrow collection procedure shall be verified or validated to determine whether they create an adverse impact anywhere in the operation.

B5 POLICIES AND PROCEDURES

B5.1 The Clinical Program shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in B4. These documents shall include all elements required by these Standards and shall address at a minimum:

B5.1.1 Donor and recipient evaluation, selection, and treatment.

B5.1.2 Donor and recipient consent.

B5.1.3 Donor and recipient confidentiality.

B5.1.4 Infection prevention and control.

B5.1.5 Administration of the preparative regimen.

B5.1.6 Administration of HPC and other cellular therapy products, including exceptional release.

B5.1.7 Administration of blood products.

B5.1.8 Facility management and monitoring.

B5.1.9 Disposal of medical and biohazard waste.

B5.1.10 Emergency and disaster plan, including the Clinical Program response.

B5.2 The Clinical Program shall maintain a detailed Standard Operating Procedures Manual.

B5.2.1 The Standard Operating Procedures Manual shall include a listing of all current Standard Operating Procedures.

B5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:

B5.3.1 A clearly written description of the objectives.

B5.3.2 A description of equipment and supplies used.

B5.3.3 Acceptable end-points and the range of expected results, where applicable.

B5.3.4 A stepwise description of the procedure.

B5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

B5.3.6 A reference section listing appropriate literature, if applicable.

B5.3.7 Documented approval of each procedure by the Clinical Program Director or designated physician prior to implementation and every two years thereafter.

B5.3.8 Documented approval of each procedural modification by the Clinical Program Director or designated physician prior to implementation.

B5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

B5.4 Copies of Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

B5.5 All personnel in the facility shall follow the Standard Operating Procedures related to their positions.

B5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.

B5.7 There shall be a process to address age-specific issues in the Standard Operating Procedures, as appropriate.

B6 ALLOGENEIC AND AUTOLOGOUS DONOR SELECTION, EVALUATION, AND MANAGEMENT

B6.1 There shall be written criteria for allogeneic and autologous donor selection, evaluation, and management by trained medical personnel.

B6.1.1 Written criteria shall include criteria for the selection of allogeneic donors who are minors.

B6.1.2 Written criteria shall include criteria for the selection of allogeneic donors when more than one donor is available and suitable.

B6.1.3 Information regarding the donation process should be provided to the potential allogeneic donor prior to HLA typing.

B6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT TO DONATE

B6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

B6.2.1.1 The risks and benefits of the procedure.

B6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

B6.2.1.3 The rights of the donor and parent of the donor who is a minor to review the results of such tests according to applicable laws and regulations.

B6.2.1.4 Alternative collection methods.

B6.2.1.5 Protection of medical information and confidentiality.

B6.2.2 The donor shall have an opportunity to ask questions.

B6.2.3 The donor shall have the right to refuse to donate.

B6.2.3.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

B6.2.4 Donor informed consent for the cellular therapy product donation shall be obtained and documented by a licensed health care professional familiar with the collection procedure.

B6.2.4.1 Informed consent from the allogeneic donor should be obtained by a licensed health care professional other than the intended recipient's primary transplant physician.

B6.2.5 In the case of a minor donor, informed consent shall be obtained from the donor's parent or legal guardian in accordance with applicable laws and regulations and shall be documented.

B6.2.6 The allogeneic donor shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and/or the recipient as appropriate.

B6.2.7 Documentation of consent shall be available to the Collection Facility staff prior to the collection procedure.

B6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

B6.3.1 There shall be criteria and evaluation procedures in place to protect the safety of donors during the process of cellular therapy product collection.

B6.3.1.1 Any abnormal finding shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

B6.3.1.2 Allogeneic donor suitability should be evaluated by a licensed health care professional who is not the primary transplant physician or health care professional overseeing care of the recipient.

B6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

B6.3.2 The risks of donation shall be evaluated and documented, including:

B6.3.2.1 Possible need for central venous access.

B6.3.2.2 Mobilization therapy for collection of HPC, Apheresis.

B6.3.2.3 Anesthesia for collection of HPC, Marrow.

B6.3.3 The donor should be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.

B6.3.4 A pregnancy assessment shall be performed for all female donors with childbearing potential within seven (7) days preceding donor mobilization, cellular therapy product collection, or initiation of the recipient's preparative regimen, whichever occurs earliest.

B6.3.5 Laboratory testing of all donors shall be performed by a laboratory accredited, registered, or licensed in accordance with applicable laws and regulations using one or more donor screening tests approved or cleared by the governmental authority.

B6.3.5.1 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.

B6.3.6 A donor advocate should be available to represent allogeneic donors who are minors or who are mentally incapacitated.

B6.3.7 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the transplant physician.

B6.3.8 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff.

B6.3.9 There shall be a policy for follow-up of donors that includes routine management and the management of collection-associated adverse events.

B6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

B6.4.1 Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

B6.4.2 A red cell antibody screen shall be performed on allogeneic donors and allogeneic recipients.

B6.4.3 Allogeneic donors shall be evaluated for risk factors that might result in disease transmission from the cellular therapy product by medical history, physical examination, examination of relevant medical records, and laboratory testing.

B6.4.4 The medical history for allogeneic donors shall include at least the following:

B6.4.4.1 Vaccination history.

B6.4.4.2 Travel history.

B6.4.4.3 Blood transfusion history.

B6.4.4.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the applicable governmental authority.

B6.4.4.5 Questions to identify persons at risk of transmitting inherited conditions.

B6.4.4.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.

B6.4.4.7 Questions to identify a past history of malignant disease.

B6.4.4.8 The allogeneic donor shall confirm that all the information provided is true to the best of his/her knowledge.

B6.4.5 Within thirty (30) days prior to collection, allogeneic HPC donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests as required by applicable laws and regulations:

B6.4.5.1 Human immunodeficiency virus, type 1.

B6.4.5.2 Human immunodeficiency virus, type 2.

B6.4.5.3 Hepatitis B virus.

B6.4.5.4 Hepatitis C virus.

B6.4.5.5 Treponema pallidum (syphilis).

B6.4.6 If required by applicable laws and regulations, allogeneic HPC donors shall also be tested within thirty (30) days prior to collection for evidence of clinically relevant infection by the following disease agents:

B6.4.6.1 Human T cell lymphotrophic virus I.

B6.4.6.2 Human T cell lymphotrophic virus II.

B6.4.6.3 West Nile Virus.

B6.4.6.4 *Trypanosoma cruzi* (Chagas' Disease).

B6.4.7 Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

B6.4.8 For viable, lymphocyte rich cells, including therapeutic cells and other cellular therapy products, each allogeneic donor shall be tested for communicable disease agents listed in B6.4.5 and B6.4.6 within seven (7) days prior to or after collection in the U.S. or 30 days prior to collection in Europe, or in accordance with applicable laws and regulations.

B6.4.9 Allogeneic donors shall be tested for CMV (unless previously documented to be positive).

B6.4.10 Allogeneic donors and recipients shall be tested at a minimum for HLA-A, B, DRB1 type by a laboratory accredited by ASHI, EFI, or equivalent. HLA-C testing shall be performed for unrelated allogeneic donors and related allogeneic donors other than siblings.

B6.4.10.1 DNA high resolution molecular typing shall be used for DRB1 typing.

B6.4.10.2 Verification typing shall be performed using an independently collected sample prior to allogeneic donor selection.

B6.4.11 Allogeneic donors shall be tested for red cell compatibility with the recipient where appropriate.

B6.4.12 Allogeneic donor eligibility, as defined by applicable laws and regulations, shall be determined by a physician after history, exam, medical record review, and testing, and shall be documented in the recipient's medical record before the recipient's preparative regimen is initiated and before the allogeneic donor begins mobilization regimen.

B6.4.13 The use of an ineligible allogeneic donor shall require documentation of the rationale for his/her selection and suitability by the transplant physician, urgent medical need documentation, and the documented informed consent of the donor and the recipient.

B6.4.14 Allogeneic donor eligibility and suitability shall be communicated in writing to the Collection and Processing Facilities.

B6.4.15 There shall be a policy covering the creation, regular review, and retention of allogeneic donor records.

B6.4.15.1 Allogeneic donor records shall include donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

B7 THERAPY ADMINISTRATION

B7.1 The attending physician shall verify the availability and suitability of a donor or cellular therapy product prior to initiating the recipient's preparative regimen.

B7.1.1 The clinical service shall notify the Processing Facility prior to requesting a cryopreserved cellular therapy product from a cord blood bank or registry.

B7.2 There shall be a policy addressing safe administration of the preparative regimen.

B7.2.1 There shall be a policy addressing safe administration of chemotherapy.

B7.2.1.1 The treatment orders shall include the patient height and weight, specific dates, daily doses (if appropriate), and route of administration of each agent.

B7.2.1.2 Preprinted orders or electronic equivalents shall be used for protocols and standardized regimens. These orders shall be verified and documented by an attending physician.

B7.2.1.3 The pharmacist preparing the chemotherapy shall verify and document the doses against the protocol or standardized regimen listed on the orders.

B7.2.1.4 Prior to administration of chemotherapy, two (2) persons qualified to administer chemotherapy shall verify and document the drug and dose in the bag or pill against the orders and the protocol, and the identity of the patient to receive the chemotherapy.

B7.2.2 There shall be a policy addressing safe administration of radiation therapy.

B7.2.2.1 There shall be a consultation with a radiation oncologist prior to initiation of therapy if radiation treatment is used in the preparative regimen.

B7.2.2.2 The patient's diagnosis, pre-existing co-morbid conditions, and proposed preparative regimen shall be made available to the consulting radiation oncologist in writing.

B7.2.2.3 A documented consultation by a radiation oncologist shall at a minimum address any prior radiation treatment the patient may

have received and any other factors that may increase the toxicity of the radiation.

B7.2.2.4 The consultation shall also include radiation planning.

B7.2.2.5 Prior to administration of each dose of radiation therapy, the dose shall be verified and documented as per radiation therapy standards.

B7.2.2.6 A final report of the details of the radiation therapy administered shall be documented in the patient medical record.

B7.3 There shall be a policy addressing safe administration of extracorporeal photopheresis (ECP).

B7.3.1 There shall be a consultation with the facility that performs ECP prior to initiation of therapy.

B7.3.2 Before ECP is undertaken, there shall be a written order from a physician specifying, at a minimum, the patient's diagnosis, proposed regimen, timing of the procedure, and any other factors that may affect the safe administration of ECP.

B7.3.3 A final report of the details of ECP administered, including an assessment of the response, shall be documented in the patient's medical record.

B7.3.4 The ECP procedure shall be performed according to written standard operating procedures of the facility performing the procedure appropriate for the clinical condition of the patient.

B7.3.5 Outcomes, including adverse events, related to the administration of ECP to patients within the Clinical Program shall be analyzed annually.

B7.4 There shall be a policy addressing safe administration of cellular therapy products.

B7.4.1 There shall be a policy for determining the appropriate volume and the appropriate dose of red blood cells, cryoprotectants, and other additives.

B7.4.1.1 Cord blood units that have not been red cell reduced shall be diluted and/or washed.

B7.4.1.2 Cord blood units that have been red cell reduced should be diluted and/or washed.

B7.4.1.3 For double cord blood transplants, the first unit shall be administered safely prior to administration of the second unit.

B7.4.2 Two (2) qualified persons shall verify the identity of the recipient and the product and the order for administration prior to the administration of the cellular therapy product.

B7.4.2.1 Verification of the identity and the order shall be documented.

B7.4.3 There shall be documentation in the patient medical record of the unit identifier and a copy of the distribution record.

B7.4.4 A circular of information for cellular therapy products shall be available to staff.

B8 CLINICAL RESEARCH

B8.1 If required by applicable laws and regulations, Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms by a process that is approved by the appropriate governmental authority.

B8.1.1 Those Clinical Programs utilizing applicable investigational treatment protocols shall have in place a pharmacy equipped for research activities, including a process for tracking, inventory, and secured storage of investigational drugs.

B8.2 Documentation for all research protocols performed by the Clinical Program shall be maintained in accordance with institutional policies and applicable laws and regulations, including all audits; documentation of approval by the Institutional Review Board, Ethics Committee, or equivalent; correspondence with regulatory agencies; and any adverse outcomes.

B8.3 For clinical research, informed consent shall be obtained from each research subject or legally authorized representative, in language he or she can understand, and under circumstances that minimize the possibility of coercion or undue influence.

B8.3.1 The research subject shall be given the opportunity to ask questions and to have his/her questions answered to his/her satisfaction, and to withdraw from the research without prejudice.

B8.3.2 Informed consent for a research subject shall contain the following elements at a minimum and comply with applicable laws and regulations:

B8.3.2.1 An explanation of the research purposes, a description of the procedures to be followed, and the identification of experimental procedures.

B8.3.2.2 The expected duration of the subject's participation.

B8.3.2.3 A description of the reasonably expected risks, discomforts, benefits to the subject or others, and alternative procedures.

B8.3.2.4 A statement of the extent to which confidentiality will be maintained.

B8.3.2.5 An explanation of the extent of compensation for injury.

B8.4 There shall be a process in place to address, as appropriate, the disclosure of any issues that may represent a conflict of interest in clinical research.

B9 DATA MANAGEMENT

B9.1 The Clinical Program shall collect all the data necessary to complete the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A forms of the EBMT.

B10 RECORDS

B10.1 Clinical Program records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained in accordance with applicable laws and regulations, or a defined program or institution policy, unless otherwise specified in these Standards.

B10.1.1 Employee records shall be maintained in a confidential manner and as required by applicable laws and regulations.

B10.2 Patient and donor records including, but not limited to, consents and records of care, shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration, whichever is latest.

B10.3 Research records shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

B10.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

B10.4.1 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

B10.4.2 The Clinical Program shall furnish to other facilities involved in the collection or processing of the cellular therapy product outcome data in so far as they concern the safety, purity, or potency of the cellular therapy product involved.

PART CM: MARROW COLLECTION FACILITY STANDARDS

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CM9 Cellular Therapy Product Storage

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PART CM: MARROW COLLECTION FACILITY STANDARDS

CM1 GENERAL

CM1.1 These Standards apply to the Marrow Collection Facility for collection activities of all cellular therapy products collected from living donors.

CM1.2 The Marrow Collection Facility shall use cell processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Marrow Collection Facility.

CM1.3 The Marrow Collection Facility shall abide by all applicable laws and regulations.

CM1.3.1 The Marrow Collection Facility shall be licensed, registered, and/or accredited as required by the appropriate governmental authority for the activities performed.

CM1.4 For initial accreditation, the Marrow Collection Facility, including a Marrow Collection Facility Medical Director and at least one staff member, shall have been in place and performing cellular therapy product collections for at least twelve (12) months preceding accreditation.

CM1.4.1 A minimum of one (1) marrow collection procedure shall have been performed in the twelve (12) months preceding accreditation.

CM1.5 The Marrow Collection Facility shall perform a minimum average of one (1) marrow collection procedure per year within the accreditation cycle.

CM2 MARROW COLLECTION FACILITY

CM2.1 There shall be appropriate designated areas for collection of cellular therapy products, for the product collected, and for storage of supplies, reagents, and equipment.

CM2.1.1 The Marrow Collection Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

CM2.1.2 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all products prior to release or distribution.

CM2.1.3 There shall be a process for confidential donor examination and evaluation.

CM2.2 The Marrow Collection Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.

CM2.3 When using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled where appropriate for temperature, humidity, ventilation, air quality, and surface contaminates.

CM2.4 Marrow Collection Facility parameters and environmental conditions shall be controlled to ensure the safety and comfort of patients, donors, and personnel.

CM2.5 The Marrow Collection Facility shall be maintained in a clean, sanitary, and orderly manner.

CM2.6 There shall be adequate equipment and materials for the procedures performed.

CM2.7 There shall be access to autologous and/or CMV-appropriate and irradiated blood products.

CM2.8 There shall be access to an intensive care unit and/or emergency services.

CM2.9 SAFETY REQUIREMENTS

CM2.9.1 The Marrow Collection Facility shall be operated in a manner designed to minimize the risks to the health and safety of employees, patients, donors, visitors, and volunteers.

CM2.9.2 The Marrow Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

CM3 PERSONNEL

CM3.1 MARROW COLLECTION FACILITY MEDICAL DIRECTOR

CM3.1.1 There shall be a Marrow Collection Facility Medical Director who is a licensed physician with postgraduate training in cell collection and/or transplantation.

CM3.1.2 The Marrow Collection Facility Medical Director or designee shall be responsible for the following elements:

CM3.1.2.1 All technical procedures.

CM3.1.2.2 Performance of the collection procedure.

CM3.1.2.3 Supervision of staff.

CM3.1.2.4 Administrative operations.

CM3.1.2.5 The medical care of allogeneic and/or autologous donors undergoing marrow collection.

CM3.1.2.6 Pre-collection evaluation of allogeneic and/or autologous donors at the time of donation.

CM3.1.2.7 Care of any complications resulting from the collection procedure.

CM3.1.2.8 The Quality Management Program, including compliance with these Standards and other applicable laws and regulations.

CM3.1.3 The Marrow Collection Facility Medical Director shall have at least one year experience in cellular therapy product collection procedures.

CM3.1.3.1 The Marrow Collection Facility Medical Director shall have performed or supervised at least ten (10) marrow collection procedures within his/her career.

CM3.1.4 The Marrow Collection Facility Medical Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

CM3.2 QUALITY MANAGEMENT SUPERVISOR

CM3.2.1 There shall be a Marrow Collection Facility Quality Management Supervisor approved by the Marrow Collection Facility Medical Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Marrow Collection Facility.

CM3.2.2 The Marrow Collection Facility Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular therapy, cell collection, and/or quality management.

CM3.3 STAFF

CM3.3.1 The Marrow Collection Facility shall have access to licensed health care professionals who are trained and competent in marrow collection.

CM3.3.2 There shall be adequate numbers of trained collection personnel available in the Marrow Collection Facility.

CM3.3.3 For Marrow Collection Facilities collecting cellular therapy products from pediatric donors, physicians and collection staff shall have documented training and experience in performing these procedures.

CM4 QUALITY MANAGEMENT

CM4.1 The Marrow Collection Facility shall comply with B4 if it operates independently of a Clinical Program.

CM5 POLICIES AND PROCEDURES

CM5.1 The Marrow Collection Facility shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in CM4. These documents shall include all elements required by these Standards and shall address at a minimum:

CM5.1.1 Donor and recipient confidentiality.

CM5.1.2 Donor consent.

CM5.1.3 Donor treatment.

CM5.1.4 Donor screening.

CM5.1.5 Management of donors, including pediatric donors if applicable.

CM5.1.6 Cellular therapy product collection.

CM5.1.7 Labeling (including associated forms and samples).

CM5.1.8 Cellular therapy product expiration dates.

CM5.1.9 Cellular therapy product storage.

CM5.1.10 Release and exceptional release.

CM5.1.11 Transportation and shipping to include methods and conditions to be used for distribution to external facilities.

CM5.1.12 Critical equipment, reagent, and supply management.

CM5.2 The Marrow Collection Facility shall comply with B5.2 if it operates independently of a Clinical Program.

CM5.3 Standard Operating Procedures required in CM5.1 shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure shall include:

CM5.3.1 A clearly written description of the objectives.

CM5.3.2 A description of equipment and supplies used.

CM5.3.3 Acceptable end-points and the range of expected results, where applicable.

CM5.3.4 A stepwise description of the procedure.

CM5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

CM5.3.6 A reference section listing appropriate literature, if applicable.

CM5.3.7 Documented approval of each procedure by the Marrow Collection Facility Medical Director, as appropriate, prior to implementation and every two years thereafter.

CM5.3.8 Documented approval of each procedural modification by the Marrow Collection Facility Medical Director or designated physician prior to implementation.

CM5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

CM5.4 Copies of Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

CM5.5 All personnel in the Marrow Collection Facility shall follow the Standard Operating Procedures related to their positions.

CM5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.

CM5.7 There shall be a process to address age-specific issues in the Standard Operating Procedures as appropriate.

CM6 ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

CM6.1 There shall be written criteria for allogeneic and autologous donor evaluation and management by trained medical personnel.

CM6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION

CM6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

CM6.2.1.1 The risks and benefits of the procedure.

CM6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

CM6.2.1.3 The rights of the donor and parent of the donor who is a minor to review the results of such tests according to applicable laws and regulations.

CM6.2.1.4 Protection of medical information and confidentiality.

CM6.2.2 The donor shall have an opportunity to ask questions.

CM6.2.3 The donor shall have the right to refuse to donate.

CM6.2.3.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

CM6.2.4 Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional familiar with the collection procedure.

CM6.2.4.1 Informed consent from the allogeneic donor should be obtained by a licensed health care professional other than the intended recipient's primary transplant physician.

CM6.2.5 In the case of a minor donor, informed consent shall be obtained from the donor's parent or legal guardian in accordance with applicable laws and regulations and shall be documented.

CM6.2.6 The allogeneic donor shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and/or the recipient as appropriate.

CM6.2.7 Documentation of consent shall be available to the Marrow Collection Facility staff prior to the collection procedure.

CM6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

CM6.3.1 There shall be criteria and evaluation procedures in place to protect the safety of donors during the process of cellular therapy product collection.

CM6.3.1.1 The Marrow Collection Facility shall ensure that any abnormal findings are reported to the donor with documentation in the donor record of recommendations made for follow-up care.

CM6.3.1.2 Allogeneic donor suitability should be evaluated by a licensed health care professional who is not the primary transplant physician or health care professional overseeing care of the recipient.

CM6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

CM6.3.2 The risks of donation shall be evaluated and documented, including:

CM6.3.2.1 Anesthesia for marrow collection.

CM6.3.3 A pregnancy assessment shall be performed for all female donors with childbearing potential within seven (7) days preceding donor mobilization, cellular therapy product collection, or initiation of the recipient's preparative regimen, whichever occurs earliest.

CM6.3.4 Laboratory testing of all donors shall be performed by a laboratory accredited, registered, or licensed in accordance with applicable laws and regulations using one or more donor screening tests approved or cleared by the governmental authority.

CM6.3.5 A donor advocate should be available to represent allogeneic donors who are minors or who are mentally incapacitated.

CM6.3.6 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the transplant physician. Collection staff shall document review of these donor safety issues.

CM6.3.7 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff. Collection staff shall document review of these issues prior to collection.

CM6.3.8 There shall be a policy for follow-up of donors that includes routine management and the management of donation-associated adverse events.

CM6.3.9 Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

CM6.3.10 A red cell antibody screen shall be performed on allogeneic donors and allogeneic recipients.

CM7 CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

CM7.1 ISBT 128 CODING AND LABELING

CM7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate modifiers and attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

CM7.1.2 If the Marrow Collection Facility has not fully implemented ISBT 128 technology, an implementation plan for the usage of ISBT 128 coding and labeling shall be in place.

CM7.2 LABELING OPERATIONS

CM7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products and product samples.

CM7.2.2 The labeling operation for pre-printed labels shall include, at a minimum, the following controls:

CM7.2.2.1 Labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Marrow Collection Facility Medical Director or designee to ensure accuracy regarding identity, content, and conformity.

CM7.2.2.2 Stocks of unused labels for different products shall be stored in a controlled manner to prevent errors.

CM7.2.2.3 Stocks of obsolete labels shall be destroyed.

CM7.2.3 Print-on-demand label systems shall be validated to ensure accuracy regarding identity, content, and conformity of labels to templates approved by the Marrow Collection Facility Medical Director or designee.

CM7.2.4 A system for label version control shall be employed.

CM7.2.4.1 Representative obsolete labels shall be archived for ten (10) years with inclusive dates of use or as defined by applicable laws and regulations.

CM7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

CM7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

CM7.2.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

CM7.2.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

CM7.2.7 The information entered on a container label shall be verified by at least two (2) staff members.

CM7.2.8 Labeling elements required by applicable laws and regulations shall be present.

CM7.2.9 All data fields on labels shall be completed.

CM7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

CM7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

CM7.2.12 The label shall be validated as reliable for storage under the conditions in use.

CM7.3 PRODUCT IDENTIFICATION

CM7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor and to all records describing the handling and final disposition of the product.

CM7.3.1.1 The cellular therapy product and donor and product samples shall be labeled with the same identifier.

CM7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.

CM7.3.2 Marrow Collection Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular therapy product.

CM7.3.2.1 Supplementary identifiers shall not obscure the original identifier.

CM7.3.2.2 The facility associated with each identifier shall be noted on the label.

CM7.4 LABEL CONTENT

CM7.4.1 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

CM7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information (COI) for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."

CM7.5 LABELING AT COMPLETION OF COLLECTION

CM7.5.1 Labeling at the end of collection shall occur before the cellular therapy product bag is removed from the proximity of the donor.

CM7.6 ACCOMPANYING DOCUMENTATION AT THE END OF COLLECTION

CM7.6.1 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix III at the time of distribution.

CM7.7 ADDITIONAL DOCUMENTATION AT OR IMMEDIATELY AFTER DISTRIBUTION

CM7.7.1 For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after the use of the product.

CM8 PROCESS CONTROLS

CM8.1 Collection of cellular therapy products shall be performed according to written collection procedures.

CM8.2 There shall be a process for inventory control that encompasses equipment, reagents, supplies, and labels.

CM8.2.1 There shall be a system to uniquely identify and track and trace all critical equipment, reagents, supplies, and labels used in the collection of cellular therapy products.

CM8.2.2 Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.

CM8.2.3 Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.

CM8.3 Equipment for the marrow collection procedure shall conform to applicable laws and regulations, where applicable.

CM8.4 There shall be written documentation of an interim assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

CM8.4.1 There shall be peripheral blood count criteria to proceed with collection.

CM8.5 Before cell collection is undertaken, there shall be a written order from a physician specifying, at a minimum, timing and goals of collection.

CM8.6 General or regional anesthesia, if required, shall be performed or supervised by a licensed, specialist-certified anesthesiologist.

CM8.7 Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.

CM8.8 The Marrow Collection Facility shall utilize a process for assessing the quality of cellular therapy products to ensure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.

CM8.8.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to ensure products meet predetermined release specifications.

CM8.8.2 Methods for collection shall employ procedures validated to result in acceptable cell viability and recovery.

CM8.9 Collection methods shall employ aseptic technique to ensure that cellular therapy products do not become contaminated during collection.

CM8.10 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.

CM8.11 Cellular therapy products shall be packaged in a closed sterile transfer pack appropriate for blood or marrow products.

CM8.12 HPC, Marrow products shall be filtered to remove particulate material prior to final packaging, distribution, or administration using filters that are non-reactive with blood.

CM8.13 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

CM9 CELLULAR THERAPY PRODUCT STORAGE

CM9.1 Marrow Collection Facilities shall establish policies for the duration and conditions of storage prior to distribution to a Processing Facility or Clinical Program.

CM10 CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

CM10.1 Procedures for transportation and shipping of the cellular therapy product shall be designed to protect the integrity of the product and the health and safety of facility personnel.

CM10.1.1 The primary cellular therapy product container shall be placed in a secondary container that is sealed to prevent leakage.

CM10.1.2 The cellular therapy product shall be transported and/or shipped to the Processing Facility at a temperature defined in the transportation and shipping procedure.

CM10.1.3 Cellular therapy products that are transported and/or shipped from the collection site to any non-contiguous Processing Facility shall be transported and/or shipped in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling.

CM10.1.4 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported by a qualified courier.

CM10.2 The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the transportation and shipping procedure and in compliance with CM7.6.

CM10.3 There shall be a record of the date and time of cellular therapy product distribution.

CM11 RECORDS

CM11.1 The Marrow Collection Facility shall comply with B10 if it operates independently of a Clinical Program.

CM12 DIRECT DISTRIBUTION TO CLINICAL PROGRAM

CM12.1 Where cellular therapy products are distributed directly from the Marrow Collection Facility to the Clinical Program for administration or subsequent processing, the Standards related to labeling, documentation, distribution, transportation, and recordkeeping in Sections D7, D8, D10, D12, and the Appendices apply.

PART C: APHERESIS COLLECTION FACILITY STANDARDS

C1 General

C2 Apheresis Collection Facility

C3 Personnel

C4 Quality Management

C5 Policies and Procedures

C6 Allogeneic and Autologous Donor Evaluation and Management

C7 Coding and Labeling of Cellular Therapy Products

C8 Process Controls

C9 Cellular Therapy Product Storage

C10 Cellular Therapy Product Transportation and Shipping

C11 Records

C12 Direct Distribution to Clinical Program

PART C: APHERESIS COLLECTION FACILITY STANDARDS

C1 GENERAL

C1.1 These Standards apply to the Apheresis Collection Facility for collection activities of all cellular therapy products collected from living donors.

C1.2 The Apheresis Collection Facility shall use cell processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Apheresis Collection Facility.

C1.3 The Apheresis Collection Facility shall abide by all applicable laws and regulations.

C1.3.1 The Apheresis Collection Facility shall be licensed, registered, and/or accredited as required by the appropriate governmental authority for the activities performed.

C1.4 For initial accreditation, the Apheresis Collection Facility, including an Apheresis Collection Facility Director, an Apheresis Collection Facility Medical Director, and at least one staff member, shall have been in place and performing cellular therapy product collections for at least twelve (12) months preceding accreditation.

C1.4.1 A minimum of ten (10) cellular therapy products shall have been collected by apheresis in the twelve (12) months preceding accreditation.

C1.5 The Apheresis Collection Facility shall collect a minimum average of ten (10) cellular therapy products by apheresis per year within the accreditation cycle.

C2 APHERESIS COLLECTION FACILITY

C2.1 There shall be appropriate designated areas for collection of cellular therapy products, for the product collected, and for storage of supplies, reagents, and equipment.

C2.1.1 The Apheresis Collection Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

C2.1.2 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all products prior to release or distribution.

C2.1.3 There shall be suitable space for confidential donor examination and evaluation.

C2.2 The Apheresis Collection Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.

C2.3 Critical Apheresis Collection Facility parameters that may affect cellular therapy product viability, integrity, contamination, sterility, or cross-contamination during collection shall be identified, controlled, monitored, and recorded to demonstrate ongoing compliance.

C2.3.1 When using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled where appropriate for temperature, humidity, ventilation, air quality, and surface contaminates.

C2.3.2 Apheresis Collection Facility parameters and environmental conditions shall be controlled to ensure the safety and comfort of patients, donors, and personnel.

C2.4 The Apheresis Collection Facility shall be maintained in a clean, sanitary, and orderly manner.

C2.4.1 There shall be documentation of facility cleaning and sanitation to ensure adequate conditions for proper operations.

C2.5 There shall be adequate equipment and materials for the procedures performed.

C2.6 There shall be access to autologous and/or CMV-appropriate and irradiated blood products.

C2.7 There shall be access to an intensive care unit and/or emergency services.

C2.8 SAFETY REQUIREMENTS

C2.8.1 The Apheresis Collection Facility shall be operated in a manner designed to minimize the risks to the health and safety of employees, patients, donors, visitors, and volunteers.

C2.8.2 The Apheresis Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

C3 PERSONNEL

C3.1 APHERESIS COLLECTION FACILITY DIRECTOR

C3.1.1 There shall be an Apheresis Collection Facility Director who is an individual with a medical degree or degree in a relevant science, qualified by postgraduate training or experience for the scope of activities carried out in the Apheresis Collection Facility. The Apheresis Collection Facility Director may also serve as the Apheresis Collection Facility Medical Director, if appropriately credentialed.

C3.1.2 The Apheresis Collection Facility Director shall be responsible for all technical procedures, performance of the collection procedure, supervision of staff, administrative operations, and the Quality

Management Program, including compliance with these Standards and other applicable laws and regulations.

C3.1.3 The Apheresis Collection Facility Director shall have at least one year experience in cellular therapy product collection procedures.

C3.1.3.1 The Apheresis Collection Facility Director shall have performed or supervised a minimum of four (4) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of four (4) cellular therapy product apheresis collection procedures per year within the accreditation cycle.

C3.1.4 The Apheresis Collection Facility Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

C3.2 APHERESIS COLLECTION FACILITY MEDICAL DIRECTOR

C3.2.1 There shall be an Apheresis Collection Facility Medical Director who is a licensed or certified physician with postgraduate training in cell collection and/or transplantation. The Apheresis Collection Facility Medical Director may also serve as the Apheresis Collection Facility Director, if appropriately credentialed.

C3.2.2 The Apheresis Collection Facility Medical Director or designee shall be responsible for the medical care of patients undergoing apheresis, including the pre-collection evaluation of the donor at the time of donation and care of any complications resulting from the collection procedure.

C3.2.3 The Apheresis Collection Facility Medical Director shall have at least one year experience in cellular therapy product collection procedures.

C3.2.3.1 The Apheresis Collection Facility Medical Director shall have performed or supervised a minimum of four (4) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of four (4) cellular therapy product apheresis collection procedures per year within the accreditation cycle.

C3.2.4 The Apheresis Collection Facility Medical Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

C3.3 QUALITY MANAGEMENT SUPERVISOR

C3.3.1 There shall be an Apheresis Collection Facility Quality Management Supervisor approved by the Apheresis Collection Facility Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Apheresis Collection Facility.

C3.3.2 The Apheresis Collection Facility Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular therapy, cell collection, and/or quality management.

C3.4 STAFF

C3.4.1 There shall be adequate numbers of trained collection personnel available in the Apheresis Collection Facility.

C3.4.2 For Apheresis Collection Facilities collecting cellular therapy products from pediatric donors, physicians and collection staff shall have documented training and experience in performing these procedures.

C4 QUALITY MANAGEMENT

C4.1 The Apheresis Collection Facility shall establish and maintain a written Quality Management Plan.

C4.2 The Quality Management Plan shall include an organizational chart of key positions, personnel, and functions within the Apheresis Collection Facility.

C4.2.1 The Quality Management Plan shall include a description of how these key personnel interact to implement the quality management activities.

C4.2.2 There shall be an Apheresis Collection Facility Director or designee who is responsible for the Quality Management Plan as it pertains to the Apheresis Collection Facility.

C4.2.2.1 The Apheresis Collection Facility Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

C4.2.2.2 The Apheresis Collection Facility Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Apheresis Collection Facility.

C4.2.2.3 The Apheresis Collection Facility Director or designee shall report on quality management activities, at a minimum, quarterly.

C4.2.2.4 The Apheresis Collection Facility Director or designee shall report on the performance of the Quality Management Plan, at a minimum, annually. This report shall also be provided to the Clinical Program Director, as applicable.

C4.3 The Quality Management Plan shall include, or summarize and reference, personnel education, experience, and training requirements for each key position in the Apheresis Collection Facility. Personnel requirements shall include at a minimum:

C4.3.1 Current job description for all staff.

C4.3.2 A system to document the following for each staff member:

C4.3.2.1 Initial qualifications.

C4.3.2.2 Orientation.

C4.3.2.3 Initial training.

C4.3.2.4 Competency for each critical function performed.

C4.3.2.5 Continued competency at least annually.

C4.3.2.6 Training and retraining.

C4.3.2.7 Provisions for continuing education.

C4.3.3 A description of minimal trainer qualifications and a uniform plan for staff training.

C4.4 The Quality Management Plan shall include, or summarize and reference, policies and procedures for development, approval, validation, implementation, review, revision, and archival for all critical processes, policies, and procedures.

C4.5 The Quality Management Plan shall include, or summarize and reference, a system for document control. The document control system shall include at a minimum the following elements:

C4.5.1 Listing of all active critical documents that shall adhere to the document control system requirements. Controlled documents shall include at a minimum:

C4.5.1.1 Policies

C4.5.1.2 Standard Operating Procedures.

C4.5.1.3 Worksheets.

C4.5.1.4 Forms.

C4.5.1.5 Labels.

C4.5.2 A procedure for preparation, approval, implementation, review, revision, and archival of all policies and procedures.

C4.5.2.1 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

C4.5.3 A standardized format for policies, procedures, worksheets, forms, and labels.

C4.5.4 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.

C4.5.5 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

C4.5.6 A system to ensure that controlled documents cannot undergo accidental or unauthorized modification.

C4.5.7 A system for document change control that includes a description of the change, the signature of the approving individual(s), approval date, and effective date.

C4.5.8 A system for the retraction of obsolete documents to prevent unintended use.

C4.5.9 A system for record creation, assembly, review, storage, archival, and retrieval.

C4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product.

C4.6.1 Agreements shall include the responsibility of the facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.

C4.6.2 Agreements shall be dated, reviewed, and renewed on a regular basis.

C4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and product efficacy, as appropriate, including at least:

C4.7.1 For HPC products intended for hematopoietic reconstitution, a process for documentation and review of time to engraftment following product administration.

C4.7.2 For other cellular therapy products, the criteria for product efficacy and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

C4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a timetable for conducting, reviewing, and reporting audits of the Apheresis Collection Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

C4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

C4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, and implement corrective actions when necessary.

C4.8.3 Audits shall include, at a minimum:

C4.8.3.1 Documentation of proper donor eligibility determination prior to start of collection procedure.

C4.8.3.2 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

C4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

C4.9.1 Notification of the recipient's physician.

C4.9.2 Investigation of cause.

C4.9.3 Follow-up of the donor, if relevant.

C4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, adverse events, biological product deviations, and complaints.

C4.10.1 Policies and procedures shall include methods for:

C4.10.1.1 Detection.

C4.10.1.2 Investigation.

C4.10.1.3 Evaluation.

C4.10.1.4 Documentation.

C4.10.1.5 Reporting.

C4.10.1.6 Corrective action.

C4.10.1.7 Follow-up for effectiveness of corrective action.

C4.10.2 Documentation of each adverse event that occurs in the Apheresis Collection Facility shall be reviewed in a timely manner by the Apheresis Collection Facility Director and/or Apheresis Collection Facility Medical Director, as appropriate.

C4.10.3 A written description of adverse events shall be made available to the donor's physician, the recipient's physician, and the Processing Facility, if appropriate.

C4.10.4 When applicable, adverse events shall be reported to appropriate regulatory agencies within the required timeframes.

C4.10.5 Deviations from Standard Operating Procedures shall be documented.

C4.10.5.1 Planned deviations shall be pre-approved by the Apheresis Collection Facility Director or designee.

C4.10.5.2 Unplanned deviations and associated corrective actions shall be reviewed by the Apheresis Collection Facility Director or designee.

C4.10.6 There shall be a defined process improvement plan that includes policies or procedures for the recognition and investigation of the cause of all issues that require corrective action.

C4.10.6.1 The implementation of corrective actions shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.

C4.10.6.2 Follow-up activities shall be conducted to determine if the corrective actions were effective.

C4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Apheresis Collection Facility's operations are interrupted.

C4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical reagents, supplies, equipment, and facilities.

C4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of critical procedures.

C4.14.1 Critical procedures shall include at least the following: collection procedures, labeling, storage, and distribution.

C4.14.2 Changes to a process shall be verified or validated to ensure that they do not create an adverse impact anywhere in the operation.

C5 POLICIES AND PROCEDURES

C5.1 The Apheresis Collection Facility shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in C4. These documents shall include all elements required by these Standards and shall address at a minimum:

C5.1.1 Donor and recipient confidentiality.

C5.1.2 Donor consent.

C5.1.3 Donor treatment.

C5.1.4 Donor screening, testing, and eligibility determination.

C5.1.5 Management of donors, including pediatric donors if applicable.

C5.1.6 Product collection.

C5.1.7 Labeling (including associated forms and samples).

C5.1.8 Product expiration dates.

C5.1.9 Product storage.

C5.1.10 Release and exceptional release.

C5.1.11 Transportation and shipping to include methods and conditions to be used for distribution to external facilities.

C5.1.12 Reagent and supply management.

C5.1.13 Equipment operation, maintenance, and monitoring to include corrective actions in the event of failure.

C5.1.14 Cleaning and sanitation procedures to include identification of the individuals responsible for the activities.

C5.1.15 Disposal of medical and biohazard waste.

C5.1.16 Facility management and monitoring.

C5.1.17 Emergency and disaster plan, including the Apheresis Collection Facility response.

C5.2 The Apheresis Collection Facility shall maintain a Standard Operating Procedures Manual.

C5.2.1 The Standard Operating Procedures Manual shall include a listing of all current Standard Operating Procedures.

C5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure shall include:

C5.3.1 A clearly written description of the objectives.

C5.3.2 A description of equipment and supplies used.

C5.3.3 Acceptable end-points and the range of expected results, where applicable.

C5.3.4 A stepwise description of the procedure.

C5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

C5.3.6 A reference section listing appropriate literature, if applicable.

C5.3.7 Documented approval of each procedure by the Apheresis Collection Facility Director or Medical Director, as appropriate, prior to implementation and every two years thereafter.

C5.3.8 Documented approval of each procedural modification by the Apheresis Collection Facility Director or designated physician prior to implementation.

C5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

C5.4 Copies of Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

C5.5 All personnel in the Apheresis Collection Facility shall follow the Standard Operating Procedures related to their positions.

C5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.

C5.7 There shall be a process to address age-specific issues in the Standard Operating Procedures as appropriate.

C6 ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

C6.1 There shall be written criteria for allogeneic and autologous donor evaluation and management by trained medical personnel.

C6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION

C6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

C6.2.1.1 The risks and benefits of the procedure.

C6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

C6.2.1.3 The rights of the donor and parent of the donor who is a minor to review the results of such tests according to applicable laws and regulations.

C6.2.1.4 Protection of medical information and confidentiality.

C6.2.2 The donor shall have an opportunity to ask questions.

C6.2.3 The donor shall have the right to refuse to donate.

C6.2.3.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

C6.2.4 Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional familiar with the collection procedure.

C6.2.4.1 Informed consent from the allogeneic donor should be obtained by a licensed health care professional other than the intended recipient's primary transplant physician.

C6.2.5 In the case of a minor donor, informed consent shall be obtained from the donor's parent or legal guardian in accordance with applicable laws and regulations and shall be documented.

C6.2.6 The allogeneic donor shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and/or the recipient as appropriate.

C6.2.7 Documentation of consent shall be available to the Apheresis Collection Facility staff prior to the collection procedure.

C6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

C6.3.1 There shall be criteria and evaluation procedures in place to protect the safety of donors during the process of cellular therapy product collection.

C6.3.1.1 The Apheresis Collection Facility shall ensure that any abnormal findings are reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

C6.3.1.2 Allogeneic donor suitability should be evaluated by a licensed health care professional who is not the primary transplant physician or health care professional overseeing care of the recipient.

C6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

C6.3.2 The risks of donation shall be evaluated and documented, including:

C6.3.2.1 Possible need for central venous access.

C6.3.2.2 Mobilization therapy for collection of HPC, Apheresis.

C6.3.3 The donor should be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.

C6.3.4 A pregnancy assessment shall be performed for all female donors with childbearing potential within seven (7) days preceding donor mobilization,

cellular therapy product collection, or initiation of the recipient's preparative regimen, whichever occurs earliest.

C6.3.5 Laboratory testing of all donors shall be performed by a laboratory accredited, registered, or licensed in accordance with applicable laws and regulations using one or more donor screening tests approved or cleared by the governmental authority.

C6.3.6 A donor advocate should be available to represent allogeneic donors who are minors or who are mentally incapacitated.

C6.3.7 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the transplant physician. Collection staff shall document review of these donor safety issues.

C6.3.8 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Apheresis Collection Facility staff. Collection staff shall document review of these issues prior to collection.

C6.3.9 There shall be a policy for follow-up of donors that includes routine management and the management of donation-associated adverse events.

C6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

C6.4.1 Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

C6.4.2 A red cell antibody screen shall be performed on allogeneic donors and allogeneic recipients.

C6.4.3 The Apheresis Collection Facility shall comply with B6.4.3 through B6.4.4.8 when primarily responsible for donor screening for transmissible disease.

C6.4.4 The Apheresis Collection Facility shall comply with B6.4.5 through B6.4.9 when primarily responsible for infectious disease testing of HPC donors.

C6.4.5 The Apheresis Collection Facility shall comply with B6.4.10 through B6.4.11 when primarily responsible for testing for the selection of allogeneic donors.

C6.4.6 The Apheresis Collection Facility shall ensure that allogeneic donor eligibility, as defined by applicable laws and regulations, is determined by a physician after history, exam, medical record review, and testing before the donor begins the mobilization regimen.

C6.4.7 Collection of a cellular therapy product from an ineligible allogeneic donor shall require documentation of urgent medical need that includes the

rationale for the selection and documentation of the informed consent of the donor and the recipient.

C6.4.8 Allogeneic donor eligibility shall be communicated in writing to the Processing Facility.

C6.5 DONOR RECORDS

C6.5.1 There shall be a policy covering the creation, regular review, and retention of donor records.

C6.5.2 Apheresis Collection Facility donor records shall include at a minimum the following:

C6.5.2.1 Donor identification including at least name and date of birth.

C6.5.2.2 Age, gender, and medical history, and, if applicable, behavioral history.

C6.5.2.3 Consent to donate.

C6.5.2.4 Results of laboratory testing.

C6.5.2.5 Donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

C7 CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

C7.1 ISBT 128 CODING AND LABELING

C7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate modifiers and attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

C7.1.2 If the Apheresis Collection Facility has not fully implemented ISBT 128 technology, an implementation plan for the usage of ISBT 128 coding and labeling shall be in place.

C7.2 LABELING OPERATIONS

C7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products and product samples.

C7.2.2 The labeling operation for pre-printed labels shall include, at a minimum, the following controls:

C7.2.2.1 Labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Apheresis Collection Facility Director or

designee to ensure accuracy regarding identity, content, and conformity.

C7.2.2.2 Stocks of unused labels for different products shall be stored in a controlled manner to prevent errors.

C7.2.2.3 Stocks of obsolete labels shall be destroyed.

C7.2.3 Print-on-demand label systems shall be validated to ensure accuracy regarding identity, content, and conformity of labels to templates approved by the Apheresis Collection Facility Director or designee.

C7.2.4 A system for label version control shall be employed.

C7.2.4.1 Representative obsolete labels shall be archived for ten (10) years with inclusive dates of use or as defined by applicable laws and regulations.

C7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

C7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

C7.2.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

C7.2.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

C7.2.7 The information entered on a container label shall be verified by at least two (2) staff members.

C7.2.8 Labeling elements required by applicable laws and regulations shall be present.

C7.2.9 All data fields on labels shall be completed.

C7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

C7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

C7.2.12 The label shall be validated as reliable for storage under the conditions in use.

C7.3 PRODUCT IDENTIFICATION

C7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor and to all records describing the handling and final disposition of the product.

C7.3.1.1 The cellular therapy product, concurrent plasma, and donor and product samples shall be labeled with the same identifier.

C7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.

C7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.

C7.3.2 Apheresis Collection Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular therapy product.

C7.3.2.1 Supplementary identifiers shall not obscure the original identifier.

C7.3.2.2 The facility associated with each identifier shall be noted on the label.

C7.4 LABEL CONTENT

C7.4.1 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

C7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information (COI) for the Use of Cellular Therapy Products, “Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States.”

C7.5 LABELING AT COMPLETION OF COLLECTION

C7.5.1 Labeling at the end of collection shall occur before the cellular therapy product bag is disconnected from the donor.

C7.6 ACCOMPANYING DOCUMENTATION AT THE END OF COLLECTION

C7.6.1 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix III at the time of distribution.

C7.7 ADDITIONAL DOCUMENTATION AT OR IMMEDIATELY AFTER DISTRIBUTION

C7.7.1 For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after the use of the product.

C8 PROCESS CONTROLS

C8.1 Collection of cellular therapy products shall be performed according to written procedures in the Apheresis Collection Facility's Standard Operating Procedures Manual.

C8.2 There shall be a process for inventory control that encompasses equipment, reagents, supplies, and labels.

C8.2.1 There shall be a system to uniquely identify and track and trace all critical equipment, reagents, supplies, and labels used in the collection of cellular therapy products.

C8.2.2 Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.

C8.2.3 Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.

C8.3 Equipment shall be standardized and calibrated on a regularly scheduled basis as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.4 Equipment shall conform to applicable laws and regulations, where applicable.

C8.5 There shall be written documentation of an interim assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

C8.5.1 A complete blood count, including platelet count, shall be performed within 24 hours prior to each HPC collection by apheresis.

C8.5.2 There shall be peripheral blood count criteria to proceed with collection.

C8.6 Before cell collection is undertaken, there shall be a written order from a physician specifying, at a minimum, timing and goals of collection.

C8.7 If required, central venous catheters shall be placed by a licensed health care professional qualified to perform the procedure.

C8.7.1 Adequacy of line placement shall be verified by the Apheresis Collection Facility.

C8.8 Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.

C8.9 The Apheresis Collection Facility shall utilize a process for assessing the quality of cellular therapy products to ensure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.

C8.9.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to ensure products meet predetermined release specifications.

C8.9.2 Methods for collection shall employ procedures validated to result in acceptable cell viability and recovery.

C8.10 Collection methods shall employ aseptic technique to ensure that cellular therapy products do not become contaminated during collection.

C8.11 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.

C8.12 Cellular therapy products shall be packaged in a closed sterile transfer pack appropriate for blood or marrow products.

C8.13 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

C9 CELLULAR THERAPY PRODUCT STORAGE

C9.1 Apheresis Collection Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of products.

C9.2 Apheresis Collection Facilities shall establish policies for the duration and conditions of storage prior to distribution to a Processing Facility or Clinical Program.

C10 CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

C10.1 Procedures for transportation and shipping of the cellular therapy product shall be designed to protect the integrity of the product and the health and safety of facility personnel.

C10.1.1 The primary cellular therapy product container shall be placed in a secondary container that is sealed to prevent leakage.

C10.1.2 The cellular therapy product shall be transported and/or shipped to the Processing Facility at a temperature defined in the Apheresis Collection Facility Standard Operating Procedure Manual.

C10.1.3 Cellular therapy products that are transported and/or shipped from the collection site to any non-contiguous Processing Facility shall be transported and/or shipped in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling.

C10.1.4 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported by a qualified courier.

C10.2 The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the Apheresis Collection Facility's Standard Operating Procedure Manual and in compliance with C7.6.

C10.3 There shall be a record of the date and time of cellular therapy product distribution.

C11 RECORDS

C11.1 GENERAL REQUIREMENTS

C11.1.1 A records management system shall be established and maintained to facilitate the review of records.

C11.1.1.1 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C11.1.1.2 For cellular therapy products that are to be distributed for use at another institution, the receiving institution shall be informed of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

C11.1.2 Records shall be maintained in such a way as to ensure their integrity and preservation.

C11.1.2.1 If records are maintained in more than one location, there shall be a system to ensure prompt identification, location, and retrieval of all records.

C11.1.2.2 Records shall be accurate, legible, and indelible.

C11.1.3 All records and communications between the collection, processing, and transplant facilities, and their patients and donors, shall be regarded as privileged and confidential.

C11.1.3.1 Safeguards to assure this confidentiality shall be established and followed in compliance with applicable laws and regulations.

C11.1.4 Records shall be maintained in one or more forms that are retrievable.

C11.2 Apheresis Collection Facility records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained in accordance with applicable laws and regulations, or a defined program or institution policy, unless otherwise specified in these Standards.

C11.2.1 Employee records shall be maintained in a confidential manner, as required by applicable laws and regulations.

C11.3 Patient and donor records including, but not limited to, consents and records of care shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration of the product, whichever is latest.

C11.4 Records to allow tracking and tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after final distribution of the product, or as required by applicable laws and regulations. These records shall include at a minimum: product identity, unique numeric or alphanumeric identifier, and collection date and time; and donor and recipient identification as far as known.

C11.5 Research records shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

C11.6 ELECTRONIC RECORDS

C11.6.1 The Apheresis Collection Facility shall establish and maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Apheresis Collection Facility that are used:

C11.6.1.1 In lieu of paper.

C11.6.1.2 To make decisions.

C11.6.1.3 To perform calculations.

C11.6.1.4 To create and/or store information used in critical procedures.

C11.6.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to ensure the accuracy, integrity, and confidentiality of all records.

C11.6.3 There shall be a means by which access to electronic records is limited to authorized individuals.

C11.6.4 The critical electronic record system shall ensure that all donor, cellular therapy product, and recipient identifiers are unique.

C11.6.5 For all critical electronic record systems, there shall be an alternative system for all electronic records that ensures continuous operation in the event that critical electronic record systems are not available. The alternative system shall be validated and Apheresis Collection Facility staff shall be trained in its use.

C11.6.6 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.

C11.6.6.1 A method shall be established or the system shall provide for review of data before final acceptance.

C11.6.6.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

C11.6.7 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

C11.6.8 For all critical electronic record systems, there shall be validated procedures for and documentation of:

C11.6.8.1 Training and continuing competency of personnel in the use of the system.

C11.6.8.2 Monitoring of data integrity.

C11.6.8.3 Back-up of the electronic records system on a regular schedule.

C11.7 RECORDS IN CASE OF DIVIDED RESPONSIBILTY

C11.7.1 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

C11.7.2 The Apheresis Collection Facility shall furnish to the facility of final disposition a copy of all records relating to the collection procedures performed in so far as they concern the safety, purity, or potency of the cellular therapy product involved.

C12 DIRECT DISTRIBUTION TO CLINICAL PROGRAM

C12.1 Where cellular therapy products are distributed directly from the Apheresis Collection Facility to the Clinical Program for administration or subsequent processing, the Standards related to labeling, documentation, distribution, transportation, and recordkeeping in Sections D7, D8, D10, D12, and the Appendices apply.

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PART D: PROCESSING FACILITY STANDARDS

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PART D: PROCESSING FACILITY STANDARDS

D1 GENERAL

D1.1 These Standards apply to all processing, storage, and distribution activities performed in the Processing Facility on cellular therapy products obtained from living donors.

D1.2 The Processing Facility shall abide by all applicable laws and regulations.

D1.2.1 The Processing Facility shall be licensed, registered, and/or accredited with the appropriate governmental authority for the activities performed.

D1.3 The Processing Facility, including a Processing Facility Director, a Processing Facility Medical Director, and at least one staff member, shall have been in place and performing cellular therapy product processing for at least twelve (12) months preceding initial accreditation.

D2 PROCESSING FACILITY

D2.1 The Processing Facility shall be of adequate space, design, and location for the intended procedures.

D2.1.1 The Processing Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

D2.1.2 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all cellular therapy products prior to release or distribution.

D2.1.3 The Processing Facility shall be secure to prevent the entrance of unauthorized personnel.

D2.1.4 The Processing Facility shall provide adequate lighting, ventilation, access to sinks, and air quality where applicable to prevent the introduction, transmission, or spread of communicable disease.

D2.2 Critical facility parameters that may affect cellular therapy product processing, storage, or distribution shall be controlled, monitored, and recorded to demonstrate ongoing compliance.

D2.3 When using processing methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled where appropriate for temperature, humidity, ventilation, air quality, and surface contaminates.

D2.3.1 Where appropriate, the Processing Facility shall provide environmental monitoring for microorganisms.

D2.4 The Processing Facility shall be maintained in a clean, sanitary, and orderly manner.

D2.5 There shall be documentation of facility cleaning and sanitation to ensure adequate conditions for proper operations.

D2.6 There shall be adequate equipment and materials for the procedures performed.

D2.7 SAFETY REQUIREMENTS

D2.7.1 The Processing Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.

D2.7.2 The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

D2.7.3 All waste generated by the Processing Facility activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable laws and regulations.

D2.7.4 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.

D3 PERSONNEL

D3.1 PROCESSING FACILITY DIRECTOR

D3.1.1 There shall be a Processing Facility Director who is an individual with a medical degree or doctoral degree in a relevant science, qualified by training or experience for the scope of activities carried out in the Processing Facility. The Processing Facility Director may also serve as the Processing Facility Medical Director, if appropriately credentialed.

D3.1.2 The Processing Facility Director shall be responsible for all procedures, administrative operations, and the Quality Management Program of the Processing Facility, including compliance with these Standards and other applicable laws and regulations.

D3.1.3 The Processing Facility Director shall participate regularly in educational activities related to the field of cellular processing and/or transplantation.

D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

D3.2.1 There shall be a Processing Facility Medical Director who is a licensed or certified physician with postgraduate training and at least one year practical and relevant experience in the preparation and clinical use of cellular therapy products. The Medical Director may also serve as the Processing Facility Director, if appropriately credentialed.

D3.2.2 The Processing Facility Medical Director or designee shall be directly responsible for all medical aspects related to the Processing Facility.

D3.2.3 The Processing Facility Medical Director shall participate regularly in educational activities related to the field of cellular processing and/or transplantation.

D3.3 QUALITY MANAGEMENT SUPERVISOR

D3.3.1 There shall be a Processing Facility Quality Management Supervisor approved by the Processing Facility Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Processing Facility.

D3.3.2 The Processing Facility Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular processing and/or quality management.

D3.4 STAFF

D3.4.1 The Processing Facility shall have an adequate number of trained staff for the volume and complexity of all operations.

D4 QUALITY MANAGEMENT

D4.1 The Processing Facility shall establish and maintain a written Quality Management Plan.

D4.2 The Quality Management Plan shall include an organizational chart of key positions, personnel, and functions within the Processing Facility.

D4.2.1 The Quality Management Plan shall include a description of how these key personnel interact to implement the quality management activities.

D4.2.2 The Processing Facility Director or designee shall be responsible for the Quality Management Plan as it pertains to the Processing Facility.

D4.2.2.1 The Processing Facility Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

D4.2.2.2 The Processing Facility Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Processing Facility.

D4.2.2.3 The Processing Facility Director or designee shall report on quality management activities, at a minimum, quarterly.

D4.2.2.4 The Processing Facility Director or designee shall report on the performance of the Quality Management Plan, at a minimum, annually. This report shall be provided to the Clinical Program Director, as applicable.

D4.3 The Quality Management Plan shall include, or summarize and reference, personnel education, experience, and training requirements for each key position in the Processing Facility. Personnel requirements shall include at a minimum:

D4.3.1 Current job description for all staff.

D4.3.2 A system to document the following for each staff member:

D4.3.2.1 Initial qualifications.

D4.3.2.2 Orientation.

D4.3.2.3 Initial training.

D4.3.2.4 Competency for each critical function performed.

D4.3.2.5 Continued competency at least annually.

D4.3.2.6 Training and retraining.

D4.3.2.7 Provisions for continuing education.

D4.3.3 A description of minimal trainer qualifications and a uniform plan for staff training.

D4.4 The Quality Management Plan shall include, or summarize and reference, policies and procedures for development, approval, validation, implementation, review, revision, and archival of all critical processes, policies, and procedures.

D4.5 The Quality Management Plan shall include, or summarize and reference, a system for document control. The document control system shall include at a minimum the following elements:

D4.5.1 Listing of all active critical documents that shall adhere to the document control system requirements. Controlled documents shall include at a minimum:

D4.5.1.1 Policies.

D4.5.1.2 Standard Operating Procedures.

D4.5.1.3 Worksheets.

D4.5.1.4 Forms.

D4.5.1.5 Labels.

D4.5.2 A procedure for preparation, approval, implementation, review, revision, and archival of all policies and procedures.

D4.5.2.1 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a

minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

D4.5.3 A standardized format for policies, procedures, worksheets, forms, and labels.

D4.5.4 Assignment of a numeric or alphanumeric identifier and title to each document and document version regulated within the system.

D4.5.5 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

D4.5.6 A system to ensure that controlled documents cannot undergo accidental or unauthorized modification.

D4.5.7 A system for document change control that includes a description of the change, the signature of approving individual(s), approval date(s), and effective date.

D4.5.8 A system for the retraction of obsolete documents to prevent unintended use.

D4.5.9 A system for record creation, assembly, review, storage, archival, and retrieval.

D4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product.

D4.6.1 Agreements shall include the responsibility of the facility performing any step in processing, testing, or storage to comply with applicable laws and regulations and these Standards.

D4.6.2 Agreements shall be dated, reviewed, and renewed on a regular basis.

D4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of cellular therapy product efficacy and/or outcome analysis, as appropriate, including at least:

D4.7.1 For HPC products intended for hematopoietic reconstitution, a process for documentation and review of time to engraftment following cellular therapy product administration.

D4.7.2 For other cellular therapy products, the criteria for product efficacy and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

D4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a timetable for conducting, reviewing, and reporting audits of the Processing Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

D4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

D4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, and implement corrective actions when necessary.

D4.8.3 Audits shall include documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

D4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

D4.9.1 Documentation and product labeling.

D4.9.2 Product quarantine.

D4.9.3 Release of the product, including identification of authorized individuals and criteria for product release.

D4.9.4 Investigation of cause.

D4.9.5 Notification of the recipient's physician, collection facility, and/or any other facility in receipt of the product, as applicable.

D4.9.6 Reporting to regulatory agencies if appropriate.

D4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, adverse events, biological product deviations, variances, and complaints.

D4.10.1 Policies and procedures shall include methods for:

D4.10.1.1 Detection.

D4.10.1.2 Investigation.

D4.10.1.3 Evaluation.

D4.10.1.4 Documentation.

D4.10.1.5 Reporting.

D4.10.1.6 Corrective action.

D4.10.1.7 Follow-up for effectiveness of corrective action.

D4.10.2 Documentation of each adverse event associated with a cellular therapy product shall be reviewed in a timely manner by the Processing Facility Director and/or Processing Facility Medical Director, as appropriate.

D4.10.3 A written description of adverse events shall be made available to the recipient's physician and the collection facility, if appropriate.

D4.10.4 When applicable, adverse events shall be reported to appropriate regulatory agencies within the required timeframes.

D4.10.5 Deviations from Standard Operating Procedures shall be documented.

D4.10.5.1 Planned deviations shall be pre-approved by the Processing Facility Director or designee and if medically relevant, by the Processing Facility Medical Director or designee.

D4.10.5.2 Unplanned deviations and associated corrective actions shall be reviewed by the Processing Facility Director or designee, or Processing Facility Medical Director or designee, as appropriate.

D4.10.6 There shall be a defined process improvement plan that includes policies or procedures for the recognition and investigation of the cause of all issues that require corrective action.

D4.10.6.1 The implementation of corrective actions shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.

D4.10.6.2 Follow-up activities shall be conducted to determine if the corrective actions were effective.

D4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

D4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Processing Facility's operations are interrupted.

D4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical supplies, reagents, equipment, and facilities.

D4.13.1 Suppliers of critical supplies, reagents, services, and equipment shall be qualified by a method that ensures they are compliant with applicable laws and regulations and these Standards.

D4.13.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

D4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of critical procedures.

D4.14.1 Critical procedures to be validated or verified shall include at least the following: processing techniques, cryopreservation procedures, labeling, storage, and distribution.

D4.14.2 There shall be documentation of review and acceptance of validation studies by the appropriate individual from Quality Management.

D4.14.3 Changes to a process shall be verified or validated to ensure that they do not create an adverse impact anywhere in the operation.

D4.14.4 Procedures for manufacturing reagents in-house shall be validated.

D5 POLICIES AND PROCEDURES

D5.1 The Processing Facility shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in D4. These documents shall include all elements required by these Standards and shall address at a minimum:

D5.1.1 Donor and recipient confidentiality.

D5.1.2 Product receipt.

D5.1.3 Processing and process control.

D5.1.4 Prevention of mix-ups and cross-contamination.

D5.1.5 Red cell compatibility testing and processing of ABO-incompatible products to include a description of the indication for and processing methods to be used for red cell and plasma depletion.

D5.1.6 Cryopreservation and thawing.

D5.1.7 Labeling (including labeling of associated forms and samples).

D5.1.8 Product expiration dates.

D5.1.9 Product storage to include alternative storage if the primary storage device fails.

D5.1.10 Release and exceptional release.

D5.1.11 Cellular therapy product recall to include a description of responsibilities and actions to be taken, including notification of appropriate regulatory agencies.

D5.1.12 Transportation and shipping, including methods and conditions within the Processing Facility and to and from external facilities.

D5.1.13 Product disposal.

D5.1.14 Reagent and supply management.

D5.1.15 Equipment operation, maintenance, and monitoring, to include corrective actions in the event of failure.

D5.1.16 Cleaning and sanitation procedures to include identification of the individuals responsible for the activities.

D5.1.17 Environmental control to include a description of environmental monitoring plan.

D5.1.18 Hygiene and use of personal protective attire.

D5.1.19 Infection control, biosafety, and chemical and radiological safety.

D5.1.20 Facility management.

D5.1.21 Decontamination and disposal of medical and biohazard waste to include Processing Facility-specific requirements where these differ from institutional requirements.

D5.1.22 Emergency and disaster plan, including the Processing Facility response.

D5.2 The Processing Facility shall maintain a detailed Standard Operating Procedures Manual.

D5.2.1 The Standard Operating Procedures Manual shall include a listing of all current Standard Operating Procedures.

D5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure shall include:

D5.3.1 A clearly written description of the objectives.

D5.3.2 A description of equipment and supplies used.

D5.3.3 Acceptable end-points and the range of expected results, where applicable.

D5.3.4 A stepwise description of the procedure.

D5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

D5.3.6 A reference section listing appropriate literature, if applicable.

D5.3.7 Documented approval of each procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and every two years thereafter.

D5.3.8 Documented approval of each procedural modification by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.

D5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

D5.4 Copies of Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

D5.5 All personnel in the Processing Facility shall follow the Standard Operating Procedures related to their positions.

D5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.

D6 PROCESS CONTROLS

D6.1 There shall be a process for controlling and monitoring the manufacturing of cellular therapy products to ensure products meet predetermined release specifications.

D6.1.1 The Processing Facility Director shall define tests and procedures for measuring and assaying cellular therapy products to ensure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the product processed.

D6.1.2 There shall be a documented system for the identification and handling of test samples so that they are accurately related to the corresponding cellular therapy product, donor, or recipient, as applicable.

D6.1.2.1 There shall be a mechanism to identify the individual obtaining the sample, the date, the time (if appropriate), and the sample source.

D6.1.2.2 Samples obtained for testing shall be representative of the cellular therapy product to be evaluated.

D6.1.3 There shall be the establishment of appropriate and validated assays and test procedures for the evaluation of cellular therapy products.

D6.1.3.1 For all cellular therapy products, a total nucleated cell count and viability measurement shall be performed.

D6.1.3.2 For HPC products, a CD34 assay shall be performed.

D6.1.3.3 For cellular therapy products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, shall be employed for evaluation of the target cell population before and after the processing procedures.

D6.1.4 For tests required by these Standards performed within the Processing Facility:

D6.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D6.1.4.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.

D6.1.4.3 Where available, reference material shall be used each day of testing and shown to give results within the defined range established for that material.

D6.1.4.4 Function checks shall be performed for testing instruments, as appropriate, prior to testing donor, recipient, or cellular therapy product samples.

D6.1.4.5 For tests performed within the Processing Facility, there shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director or designee and outcomes reviewed with the staff.

D6.1.5 Tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory certified or accredited by the appropriate laboratory regulatory agency.

D6.1.6 Communicable disease testing required by these Standards shall be performed using test reagents or kits approved by the appropriate regulatory authority and performed in an appropriately registered laboratory that is accredited or licensed in accordance with applicable laws and regulations.

D6.1.7 Cellular therapy products that do not meet release or donor eligibility requirements shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director or other designated physician.

D6.1.7.1 Notification of the transplant physician of nonconforming cellular therapy products and approval for their release shall be documented.

D6.2 There shall be a written request from the recipient's physician before processing is initiated specifying the cellular therapy product type, recipient and donor identifiers, the type of processing that is to be performed, and the anticipated date of processing.

D6.3 For allogeneic cellular therapy products, information required by the Processing Facility prior to distribution of the product shall include:

D6.3.1 A statement of donor eligibility.

D6.3.2 For ineligible donors, the reason for their ineligibility.

D6.3.3 Documentation of urgent medical need and physician approval for use, if applicable.

D6.4 For cryopreserved products received from another facility, the Processing Facility shall ensure availability of adequate storage space at the appropriate temperature.

D6.5 Processing procedures shall be validated in the Processing Facility and documented to result in acceptable target cell viability and recovery.

D6.5.1 Published validated processes shall be verified within the Processing Facility prior to implementation.

D6.5.2 The Processing Facility shall use validated methods for preparation of cellular therapy products for administration.

D6.5.2.1 If the Processing Facility lacks experience with the type of cellular therapy product requested for a recipient, personnel shall obtain the manufacturer's instructions and follow these instructions to the extent possible.

D6.5.2.2 The Processing Facility should verify the processing procedures utilizing practice units similar to the cellular therapy product intended for administration when feasible.

D6.6 Critical control points and associated assays shall be identified and performed on each cellular therapy product as defined in Standard Operating Procedures.

D6.7 Methods for processing shall employ aseptic technique and cellular therapy products shall be processed in a manner that minimizes the risk of cross-contamination.

D6.7.1 Where processing of tissues and cells involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.

D6.7.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.

D6.8 Equipment, supplies, and reagents used to process cellular therapy products shall be used in a manner that prevents product mix-ups, contamination, and cross-contamination, and that does not compromise product function and integrity.

D6.9 Supplies and reagents used in processing, testing, cryopreservation, and storage shall be controlled by a materials management system that includes requirements for:

D6.9.1 Visual examination of each supply and reagent used to manufacture cellular therapy products for damage or evidence of contamination upon receipt and acceptance into inventory.

D6.9.2 Records of receipt that shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and, as applicable, the expiration date.

D6.9.3 Storage of materials under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix up or unintended use.

D6.9.4 The use of supplies and reagents coming into contact with cellular therapy products during processing, storage, and/or administration that are sterile and of the appropriate grade for the intended use.

D6.9.4.1 Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure verified to remove infectious agents.

D6.9.5 The use of supplies and reagents in a manner consistent with instructions provided by the manufacturer.

D6.9.6 A process to prevent the use of expired reagents and supplies.

D6.10 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products.

D6.10.1 The system shall identify each cellular therapy product for which the equipment was used.

D6.11 Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, disinfection, calibration, and maintenance at prescribed intervals.

D6.11.1 The equipment shall be inspected for cleanliness prior to each use and verified to be in compliance with the maintenance schedule daily prior to use.

D6.12 The equipment shall be standardized and calibrated on a regularly scheduled basis as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.12.1 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

D6.12.2 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products manufactured during the period of uncertainty.

D6.13 There shall be a procedure that addresses the actions to take in the event of equipment malfunction or failure.

D6.14 Equipment shall conform to applicable laws and regulations.

D6.15 The Processing Facility shall monitor and document microbial contamination of cellular therapy products after processing, as specified in Standard Operating Procedures.

D6.15.1 The results of microbial cultures shall be reviewed by the Processing Facility Director or designee in a timely manner.

D6.15.2 The recipient's physician shall be notified in a timely manner of any positive microbial cultures.

D6.16 Records shall be made concurrently with each step of the processing, testing, cryopreservation, storage, and administration or disposal/disposition/distribution of each cellular therapy product in such a way that all steps may be accurately traced.

D6.16.1 Records shall identify the person immediately responsible for each significant step, including dates and times of various steps, where appropriate.

D6.16.1.1 The Processing Facility shall maintain records of identification codes of personnel including methods to link the name and/or signature to the initials or other identification codes used in other documents and records. These records shall include dates of employment.

D6.16.2 Records shall show the test results and the interpretation of each result, where appropriate.

D6.17 Lot numbers, expiration dates, and manufacturers of critical reagents and supplies and identification of key equipment used in each procedure shall be documented.

D6.18 The Processing Facility Director or designee shall review the processing record for each cellular therapy product prior to release or distribution.

D6.18.1 The recipient's physician and the Processing Facility Medical Director shall be notified when the clinically relevant processing end-points are not met.

D6.18.2 Notification and appropriate remedial actions, if taken, shall be documented in the processing record.

D6.19 Processing using more-than-minimal manipulation shall only be performed with Institutional Review Board or Ethics Committee approval, with the written informed consent of the recipient of the cellular therapy product, and in compliance with applicable laws and regulations.

D6.20 For allogeneic cellular therapy products containing red blood cells at the time of administration:

D6.20.1 Results for ABO group and Rh type testing shall be available from two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

D6.20.2 Results for a red cell antibody screen shall be available.

D6.21 One or more aliquots representing the cryopreserved cellular therapy product shall be stored.

D6.21.1 Aliquot(s) from cryopreserved cellular therapy products shall be stored under conditions that ensure a valid representation of the clinical product.

D6.21.2 For cryopreserved cellular therapy products with low volume and/or low cellular content when the storage of product aliquots is not feasible, a cryopreserved sample representing the final steps of processing shall be stored and available for future testing.

D6.21.3 Cryopreserved aliquots shall be retained according to institutional Standard Operating Procedures.

D7 CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

D7.1 ISBT 128 CODING AND LABELING

D7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate modifiers and attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

D7.1.2 If the Processing Facility has not fully implemented ISBT 128 technology, an implementation plan for the usage of ISBT 128 coding and labeling shall be in place.

D7.2 LABELING OPERATIONS

D7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products and product samples.

D7.2.2 The labeling operation for pre-printed labels shall include, at a minimum, the following controls:

D7.2.2.1 Labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Processing Facility Director or designee to ensure accuracy regarding identity, content, and conformity.

D7.2.2.2 Stocks of unused labels for different cellular therapy products shall be stored in a controlled manner to prevent errors.

D7.2.2.3 Stocks of obsolete labels shall be destroyed.

D7.2.3 Print-on-demand label systems shall be validated to ensure accuracy regarding identity, content, and conformity of labels to templates approved by the Processing Facility Director or designee.

D7.2.4 A system for label version control shall be employed.

D7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years with inclusive dates of use or as defined by applicable laws and regulations.

D7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

D7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

D7.2.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

D7.2.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

D7.2.7 The information entered on a container label shall be verified by at least two (2) staff members prior to distribution of the cellular therapy product.

D7.2.8 Labeling elements required by applicable laws and regulations shall be present.

D7.2.9 All data fields on labels shall be completed.

D7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

D7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

D7.2.12 The label shall be validated as reliable for storage under the conditions in use.

D7.3 PRODUCT IDENTIFICATION

D7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any product to its donor and to all records describing the handling and final disposition of the product.

D7.3.1.1 The cellular therapy product, concurrent plasma, and donor and product samples shall be labeled with the same identifier.

D7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.

D7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.

D7.3.2 The Processing Facility may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular therapy product.

D7.3.2.1 Supplementary identifiers shall not obscure the original identifier.

D7.3.2.2 The facility associated with each identifier shall be noted on the label.

D7.4 LABEL CONTENT

D7.4.1 Each label shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

D7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."

D7.5 PARTIAL LABEL

D7.5.1 If the cellular therapy product container is capable of bearing only a partial label, the container shall have affixed, at a minimum, the unique numeric or alphanumeric identifier of the product, the proper name of the product, the appropriate product modifiers, and, if known, the name and identifier of the intended recipient.

D7.5.2 Minimally, the information required in D7.5.1 shall be present on the cellular therapy product during all stages of processing.

D7.5.3 Any container bearing a partial label shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.

D7.6 LABELING AT COMPLETION OF PROCESSING

D7.6.1 At the end of processing, the label on the cellular therapy product container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

D7.7 LABELING AT DISTRIBUTION

D7.7.1 At the time of distribution, the label on the cellular therapy product container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

D7.7.2 The name and address of the facility that determines that the cellular therapy product meets release criteria and the name and address of the facility that makes the product available for distribution shall either appear on the product label or accompany the product at distribution.

D7.8 ACCOMPANYING DOCUMENTATION AT DISTRIBUTION

D7.8.1 Products collected in or designated for use in the U.S. shall have the elements in the Accompanying Documents at Distribution table in Appendix III accompany the cellular therapy product when it leaves the Processing Facility.

D7.9 DOCUMENTATION IMMEDIATELY AFTER DISTRIBUTION

D7.9.1 For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination.

D8 DISTRIBUTION

D8.1 PROCESSING, TRACKING, AND RELEASE CRITERIA

D8.1.1 The processing, collection, and transport or shipping records for each cellular therapy product shall be reviewed by the Processing Facility Director or designee for compliance with Standard Operating Procedures and applicable laws and regulations prior to product release or distribution.

D8.1.1.1 Records shall demonstrate trackability from the donor to the recipient and traceability from the recipient to the donor.

D8.1.2 Each cellular therapy product shall meet pre-determined release criteria prior to distribution from the Processing Facility. The release criteria shall include donor eligibility determination for allogeneic products.

D8.1.2.1 The Processing Facility Director or designee shall give specific authorization for release when the cellular therapy product does not meet technical release criteria.

D8.1.2.2 The Processing Facility Medical Director or designee shall give specific authorization for release when the cellular therapy product does not meet clinically relevant release criteria.

D8.1.2.3 Documentation of agreement of the Processing Facility Medical Director or designee and the recipient's physician consent to use any non-conforming product shall be retained in the processing record.

D8.1.3 Each cellular therapy product issued for administration shall be visually inspected by two (2) trained personnel immediately before release to verify the integrity of the product container and appropriate labeling.

D8.1.3.1 A cellular therapy product shall not be released when the container is compromised and/or recipient or donor information is not verified unless the Processing Facility Director or designee gives specific authorization for the product's release.

D8.2 DISTRIBUTION RECORDS

D8.2.1 The cellular therapy product processing records shall contain a written or printed record of product distribution including, at a minimum:

D8.2.1.1 The distribution date and time.

D8.2.1.2 Unique identifier of the intended recipient.

D8.2.1.3 The proper product name and identifier.

D8.2.1.4 Documentation of donor eligibility determination.

D8.2.1.5 Identification of the facility that distributed the product.

D8.2.2 The distribution record shall include documentation of:

D8.2.2.1 The identity of the individual who accepted the cellular therapy product.

D8.2.2.2 The date and time of receipt.

D8.3 CIRCULAR OF INFORMATION

D8.3.1 For each type of cellular therapy product, the Processing Facility shall maintain and distribute or make a document available to clinical staff containing the following as appropriate:

D8.3.1.1 The use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

D8.3.1.2 Instructions for handling the cellular therapy product to minimize the risk of contamination or cross-contamination.

D8.3.1.3 Appropriate warnings related to the prevention of the transmission or spread of communicable diseases.

D8.4 RETURN OF CELLULAR THERAPY PRODUCTS FROM ISSUE

D8.4.1 Cellular therapy products accepted for return shall meet the following criteria:

D8.4.1.1 The integrity of the primary container has not been compromised.

D8.4.1.2 The cellular therapy product has been maintained, subsequent to issue, at the specified temperature range during storage and shipping or transportation.

D8.4.2 If the criteria in Standards D8.4.1.1 and D8.4.1.2 have not been met, the Processing Facility shall not return the product to inventory unless the Processing Facility Director or designee gives specific authorization.

D8.4.3 The Processing Facility Director or designee shall consult with the recipient's physician regarding reissue or disposal of the returned product.

D8.4.4 Documentation of the events requiring return, the results of inspection upon return, and subsequent action taken to ensure product safety and viability shall be maintained in the Processing Facility records.

D9 STORAGE

D9.1 Processing Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products.

D9.2 STORAGE DURATION

D9.2.1 Processing Facilities, in consultation with the Clinical Program, shall establish policies for the duration and conditions of storage and indications for disposal.

D9.2.1.1 Patients, donors, and associated Clinical Programs should be informed about these policies before the cellular therapy product collection.

D9.2.2 Processing Facilities processing, storing, and/or releasing cellular therapy products for administration shall assign an expiration date and time, as appropriate, for non-cryopreserved products and for products thawed after cryopreservation.

D9.3 TEMPERATURE

D9.3.1 Storage temperatures shall be defined in Standard Operating Procedures.

D9.3.2 Noncryopreserved cellular therapy products shall be maintained within a specific temperature range to maintain viability and function, to inhibit infectious agents, and for a period of time not to exceed that specified in Standard Operating Procedures.

D9.3.3 Cryopreserved cellular therapy products shall be stored within a temperature range, as defined in Standard Operating Procedures, that is appropriate for the product and cryoprotectant solution used.

D9.4 PRODUCT SAFETY

D9.4.1 Materials that may adversely affect cellular therapy products shall not be stored in the same refrigerators or freezers as the cellular therapy products.

D9.4.2 For cellular therapy products immersed in liquid nitrogen, procedures to minimize the risk of cross-contamination of products shall be employed.

D9.4.3 Processing Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination as required by applicable laws and regulations.

D9.4.3.1 All cellular therapy products with positive infectious disease test results for relevant communicable disease agents and/or positive microbial cultures shall be quarantined.

D9.4.3.2 Processes for storing cellular therapy products in quarantine shall be defined in Standard Operating Procedures.

D9.4.3.3 Quarantined cellular therapy products shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.

D9.5 MONITORING

D9.5.1 Refrigerators and freezers used for storage where cellular therapy products are not fully immersed in liquid nitrogen shall have a system to monitor the temperature continuously and to record the temperature at least every four (4) hours.

D9.5.2 There shall be a mechanism to ensure that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to assure that cellular therapy products remain within the specified temperature range.

D9.6 ALARM SYSTEMS

D9.6.1 Storage devices for cellular therapy products or reagents for cellular therapy product processing shall have alarm systems that are continuously active.

D9.6.2 Alarm systems shall have audible signals or other effective notification methods.

D9.6.3 Alarm systems shall be checked periodically for function.

D9.6.4 If trained personnel are not always present in the immediate area of the storage device, a system shall be in place that alerts responsible personnel of alarm conditions on a 24-hour basis.

D9.6.5 Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.

D9.6.6 Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.

D9.6.6.1 Instructions shall include a procedure for notifying processing personnel.

D9.6.6.2 Instructions shall outline procedures to follow to ensure that cellular therapy products are maintained at safe temperatures and the process for documentation of any corrective actions in order to maintain integrity of the products.

D9.6.7 Additional storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.

D9.7 SECURITY

D9.7.1 The storage device shall be located in a secure area and accessible only to authorized personnel.

D9.8 INVENTORY CONTROL

D9.8.1 The Processing Facility shall use an inventory control system to document the availability and identity of critical reagents and supplies. This shall include:

D9.8.1.1 A system to uniquely identify and track all critical reagents and supplies used to manufacture cellular therapy products.

D9.8.1.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

D9.8.1.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

D9.8.2 The Processing Facility shall use an inventory control system to identify the location of each cellular therapy product and associated sample aliquots. The inventory control system records shall include:

D9.8.2.1 Cellular therapy product proper name or specimen name.

D9.8.2.2 Cellular therapy product unique identifier.

D9.8.2.3 Recipient name or unique identifier.

D9.8.2.4 Storage device identifier.

D9.8.2.5 Location within the storage device.

D10 TRANSPORTATION, SHIPPING, AND RECEIPT

D10.1 Procedures shall be established and maintained for transportation, shipping, and receipt of cellular therapy products.

D10.2 Procedures for transportation and shipping of cellular therapy products shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area and shall follow the applicable laws and regulations.

D10.2.1 The primary product container for non-frozen cellular therapy products shall be placed in a secondary container and sealed to prevent leakage.

D10.3 Cellular therapy products that require a temperature-controlled environment and that are transported or shipped over an extended period of time shall be transported or shipped in a container validated to maintain the appropriate temperature range.

D10.3.1 During transportation or shipping, the cellular therapy product temperature shall be maintained at the transport or shipping temperature specified by the receiving facility.

D10.4 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

D10.4.1 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

D10.4.2 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.

D10.4.3 The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transport or shipping.

D10.4.3.1 The temperature of shipping containers bearing cryopreserved cellular therapy products shall be continuously monitored during shipping.

D10.4.3.2 The shipping facility shall maintain a record of the temperature over the period of travel.

D10.4.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II.

D10.4.5 There shall also be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II.

D10.4.6 The outer container shall be labeled in accordance with applicable laws and regulations regarding the cryogenic material used and the transport or shipment of biological materials.

D10.5 METHOD OF TRANSPORTATION AND SHIPPING

D10.5.1 The transit time shall be within time limits determined by the receiving and/or distributing facility to maintain cellular therapy product safety.

D10.5.2 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported by a qualified courier.

D10.5.3 There shall be plans for alternative means of transport or shipping in an emergency.

D10.5.4 The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

D10.6 RECEIPT

D10.6.1 Procedures shall be established and maintained for acceptance, rejection, and quarantine of cellular therapy products.

D10.6.2 The receipt of each cellular therapy product shall include inspection to verify the integrity of the product container, the appearance of the product, and appropriate labeling, and to evaluate for evidence of microbial contamination.

D10.6.3 There shall be procedures to verify that the cellular therapy product was appropriately transported or shipped.

D10.6.3.1 The receiving facility shall document the temperature of the outer container upon arrival.

D10.6.3.2 For cryopreserved cellular therapy products, receiving facility records shall include documentation of the outer container temperature during shipping.

D10.6.4 The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor suitability and eligibility.

D10.6.5 There shall be procedures to maintain cellular therapy products in quarantine until they have been determined to meet criteria for release from quarantine.

D10.7 TRANSPORTATION AND SHIPPING RECORDS

D10.7.1 Transportation and shipping records shall permit tracing of the cellular therapy product from one facility to another.

D10.7.2 Transportation and shipping records shall include:

D10.7.2.1 Date and time cellular therapy product was distributed.

D10.7.2.2 Date and time cellular therapy product was received.

D10.7.2.3 Identity of the transporting or shipping facility.

D10.7.2.4 Identity of the receiving facility.

D10.7.2.5 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.

D10.7.2.6 Identity of the courier.

D10.7.2.7 Documentation of any delay or problems incurred during transportation or shipping.

D11 DISPOSAL

D11.1 Disposal of cellular therapy products shall include the following requirements:

D11.1.1 A pre-collection written agreement between the storage facility and the designated recipient or the donor, as appropriate, defining the length of storage and the circumstances for disposal of cellular therapy products.

D11.1.2 The option to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

D11.1.3 Documentation of designated recipient's death or no further need for the cellular therapy product before any product is discarded.

D11.1.4 Approval by the Processing Facility Medical Director or the recipient's physician for cellular therapy product discard or other disposition, and method of disposal.

D11.1.5 A method of disposal and decontamination that meets applicable laws and regulations for disposal of biohazardous materials and/or medical waste.

D11.2 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the patient is lost to follow-up, the storage facility shall:

D11.2.1 Communicate with the designated recipient's physician about continuing need for storage of the cellular therapy product.

D11.2.2 Make a documented effort to notify the donor or designated recipient about product disposition, including disposal or transfer.

D11.3 The records for discarded or transferred cellular therapy products shall indicate the product was discarded or transferred, date of discard or transfer, disposition, and method of disposal or transfer.

D12 RECORDS

D12.1 GENERAL REQUIREMENTS

D12.1.1 A records management system shall be established and maintained to facilitate the review of records pertaining to a particular cellular therapy product prior to distribution and for follow-up evaluation or investigation.

D12.1.1.1 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

D12.1.1.2 For cellular therapy products that are to be distributed for use at another institution, the receiving institution shall be informed of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

D12.1.2 Records shall be maintained in such a way as to ensure their integrity and preservation.

D12.1.2.1 If records are maintained in more than one location, there shall be a system to ensure prompt identification, location, and retrieval of all records.

D12.1.2.2 Records shall be accurate, legible, and indelible.

D12.1.3 All records and communications between the collection, processing, and transplant facilities, and their recipients and donors, shall be regarded as privileged and confidential.

D12.1.3.1 Safeguards to assure this confidentiality shall be established and followed in compliance with applicable laws and regulations.

D12.1.4 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

D12.1.5 Employee records shall be maintained in a confidential manner as required by applicable laws and regulations.

D12.1.6 Records shall be maintained in one or more forms that are retrievable.

D12.1.6.1 Equipment to make the records available and legible shall be readily accessible.

D12.2 ELECTRONIC RECORDS

D12.2.1 The Processing Facility shall establish and maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Processing Facility that are used:

D12.2.1.1 In lieu of paper.

D12.2.1.2 To make decisions.

D12.2.1.3 To perform calculations.

D12.2.1.4 To create and/or store information used in critical procedures.

D12.2.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to ensure the accuracy, integrity, identity, and confidentiality of all records.

D12.2.2.1 There shall be a means by which access to electronic records is limited to authorized individuals.

D12.2.2.2 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

D12.2.2.3 All critical electronic record systems shall ensure that all donor, cellular therapy product, and recipient identifiers are unique.

D12.2.3 For all critical electronic record systems, there shall be an alternative system for all electronic records that ensures continuous operation of the Processing Facility in the event that critical electronic record systems are not available. The alternative system shall be validated and Processing Facility staff shall be trained in its use.

D12.2.4 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.

D12.2.4.1 A method shall be established or the system shall provide for review of data before final acceptance.

D12.2.4.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

D12.2.5 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

D12.2.6 For all critical electronic record systems, there shall be validated procedures for and documentation of:

D12.2.6.1 Systems development.

D12.2.6.2 Numerical designation of system versions, if applicable.

D12.2.6.3 Prospective validation of system, including hardware, software, and databases.

D12.2.6.4 Installation of the system.

D12.2.6.5 Training and continued competency of personnel in systems use.

D12.2.6.6 Monitoring of data integrity.

D12.2.6.7 Back-up of the electronic records system on a regular schedule.

D12.2.6.8 System maintenance and operations.

D12.2.7 All system modifications shall be authorized, documented, and validated prior to implementation.

D12.3 RECORDS TO BE MAINTAINED

D12.3.1 Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after final distribution of the product, or as required by applicable laws and regulations. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product identity, and donor and recipient information as found on the original container.

D12.3.2 Processing Facility records related to quality control, personnel training or competency, facility maintenance, facility management, or other general facility issues shall be retained for a minimum of ten (10) years by the Processing Facility, or longer in accordance with applicable laws or regulations, or with a defined program or institution policy, unless otherwise specified in these Standards.

D12.3.2.1 Facility maintenance records pertaining to facility cleaning and sanitation shall be retained for at least three (3) years. All other facility maintenance records shall be retained as in D12.3.2.

D12.3.3 All records pertaining to the processing, testing, storage, or distribution of cellular therapy products shall be maintained for a minimum of ten (10) years after the date of administration, or if the date of administration is not known, then a minimum of ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is most recent, or according to applicable laws and regulations or institutional policy, whichever requires the longest maintenance period. The following records shall be maintained:

D12.3.3.1 Processing records.

D12.3.3.2 Compatibility test records.

D12.3.3.3 Cryopreservation records.

D12.3.3.4 Distribution records.

D12.3.3.5 Records of errors, accidents, adverse events, adverse reactions, and complaints.

D12.3.3.6 All quality management records.

D12.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

D12.4.1 If two (2) or more facilities participate in the collection, processing, or distribution of the cellular therapy product, the records of the Processing Facility shall show plainly the extent of its responsibility.

D12.4.2 The Processing Facility shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a cellular therapy product.

D12.4.3 There shall be a system to allow the Processing Facility access to information that tracks and traces all manufacturing steps performed by other facilities. This tracking and tracing system shall comply with D4.11.

D12.4.4 The Processing Facility shall furnish to the facility of final disposition a copy of all records relating to the collection, processing, and storage procedures performed in so far as they concern the safety, purity, or potency of the cellular therapy product involved.

APPENDIX I

CELLULAR THERAPY PRODUCT LABELING

Each label shall include at least the elements detailed in the following table:

Element[3]	Partial label	Label at completion of collection	Label at completion of processing	Label at distribution for administration[2]
Unique numeric or alphanumeric identifier	AF	AF	AF	AF
Proper name of product [1]	AF	AF	AF	AF
Product modifiers [1]	AF		AF	AF
Product attributes (manipulations) [1]			AC	AC
Recipient name and identifier (if applicable)	AF	AT	AT	AT
Identity and address of collection facility or donor registry		AT	AC	AC
Date, time collection ends, and (if applicable) time zone		AT	AC	AC
Approximate volume		AT	AT	AT
Name and volume or concentration of anticoagulant and other additives		AT	AT	AT
Donor identifier and (if applicable) name		AT	AT	AT
Recommended storage temperature range		AT	AT	AT
Biohazard and/or Warning Labels (as applicable, see CM7.4, C7.4, D7.4).		AT	AT	AT
If applicable: Statement “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” Statement “WARNING: Advise Patient of Communicable Disease Risks” Statement “WARNING: Reactive Test Results for [name of disease agent or disease]”		AT AT AT	AT AT AT	AT AT AT
Identity and address of processing and distribution facility(ies)			AC	AC
Statement “Do Not Irradiate”			AT	AT
Expiration Date (if applicable)			AT	AT
Expiration Time (if applicable)			AC	AT
ABO and Rh of donor (if applicable)			AC	AC
RBC compatibility testing results (if applicable)				AC
Statement "Properly Identify Intended Recipient and Product"				AT
Statement indicating that leukoreduction filters should not be used.				AT
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)		AT	AT	AT
Statement “For Use By Intended Recipient Only" (if for allogeneic recipient)				AT
Statement “For Nonclinical Use Only” (if applicable)				AT
Date of distribution				AC

AF=Affix, AT=Attach or Affix, AC=Accompany, Attach or Affix

[1]Product proper names, modifiers, and attributes (manipulations) are listed in Chapter Three of the *ISBT 128* Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. *Available at: www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.*

[2]Products thawed at the bedside do not require a new label.

[3]Facilities registered with ICCBBA, Inc. who have fully implemented *ISBT 128* labeling shall follow the *ISBT 128* Standard for the location of information on the label and/or the accompanying documentation.

APPENDIX II

CELLULAR THERAPY PRODUCT LABELS FOR SHIPPING AND TRANSPORT ON PUBLIC ROADS

Each container for shipping and transport on public roads shall include a document on the inside of the container and a label on the exterior of the container with at least the elements detailed in the following table:

Element	Inner container document	Outer container label
Date of distribution and time, if appropriate	AC	AF
Statement “Do Not X-Ray” and /or “Do Not Irradiate”, if applicable	AC	AF
Statements ”Human Cells for Administration” or equivalent and “Handle with Care”	AC	AF
Shipper handling instructions	AC	AF
Shipping facility name, street address, contact person, and phone number	AC	AF
Receiving facility name, street address, contact person, and phone number	AC	AF
Biohazard and/or Warning Labels (as applicable, see CM7.4, C7.4, D7.4).	AC	
If applicable: Statement “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” Statement “WARNING: Advise Patient of Communicable Disease Risks” Statement “WARNING: Reactive Test Results for [name of disease agent or disease]”	AC AC AC	

AC= Accompany on a single document, AF=Affix

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APPENDIX III

ACCOMPANYING DOCUMENTS AT DISTRIBUTION

Products collected in or designated for use in the U.S. shall be accompanied upon leaving the Collection or Processing Facility with at least the elements detailed in the following table:

Documentation	Allogeneic Donors-Eligible	Allogeneic Donor-Ineligible[1]	Allogeneic Donor-Incomplete[1]	Autologous Donors[5]
Statement that the donor has been determined to be either eligible or ineligible, based upon results of donor screening and testing	X	X		X (if positive)
Summary of records used to make the donor-eligibility determination[2]	X	X		X (if positive)
Name and address of the establishment that made the donor-eligibility determination	X	X		X (if positive)
Listing and interpretation of the results of all communicable disease testing performed	X	X	X	X (if positive)
Statement that the communicable disease testing was performed by a laboratory meeting regulatory requirements[3]	X	If applicable	If applicable	If applicable
Statement noting the reason(s) for the determination of ineligibility		X		If applicable
Statement that the donor-eligibility determination has not been completed			X	
Statement that the product must not be transplanted or infused until completion of the donor-eligibility determination, except under condition of urgent medical need			X	
Listing of any required screening or testing that has not yet been completed			X	
Results of donor screening that has been performed			X	
Documentation that the physician using the cellular therapy product was notified of incomplete testing or screening			X	
Instructions for product use to prevent the introduction, transmission, or spread of communicable diseases	X	X	X	X
Instructions for reporting serious adverse reactions or events to the distributing facility[4]	X	X	X	X

[1] May only be distributed after release by the Processing Facility Medical Director due to urgent medical need. For ineligible cellular therapy products or incomplete donor eligibility determination, the product must be shipped in quarantine. For products distributed prior to completion of donor eligibility, you must complete the determination and inform the physician of the results.

[2] Access (electronic or otherwise) to the source documents by the distributing facility and/or receiving facility is sufficient.

[3] Includes laboratories certified under CLIA of 1988, as amended from time to time, those that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services, or those that have met equivalent non-U.S. requirements.

[4] Access to the Clinical Program SOPs and forms could suffice when the distributing and clinical facilities are within the same building.

[5] For autologous donors, a donor eligibility determination is not required by FDA. However, if any donor screening or testing is performed and risk factors or reactive test results are identified, accompanying documentation must be provided.

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ACKNOWLEDGEMENTS

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